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Original Submission

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CLAUSEN ELY, JR.
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February 12, 1999

VIA HAND DELIVERY

Office of Premarket Approval (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, D.C. 20204

Re: GRAS Notification for the Use of Hydrogen Peroxide in the Preparation of Dehydrated Onions

To whom it may concern:

On behalf of our client, Basic Vegetable Products, L.P., 700 Airport Drive, King City, California, 93930, we submit this notification containing data and information demonstrating that hydrogen peroxide is generally recognized as safe (GRAS) when used in an aqueous solution at concentrations up to 10% in the preparation of dehydrated onions. We are submitting this notification in accordance with proposed 21 C.F.R. § 170.36 (62 *Fed. Reg.* 18960 (April 17, 1997)). In accordance with that proposed rule, we are submitting an original and two copies of the notification. We are also enclosing an additional copy of this letter to be date-stamped and returned to us to acknowledge your receipt of this notification.

Please contact me should you have any questions regarding this document.

Sincerely,

Clausen Ely, Jr.

Enclosures
cc: John Barnecut, Esq.
Mr. Ted Berner

000002

1999 FEB 17 A 8:30

[redacted]

GENERALLY RECOGNIZED AS SAFE (GRAS) NOTIFICATION FOR THE USE OF HYDROGEN PEROXIDE IN THE PREPARATION OF DEHYDRATED ONIONS

Submitted on behalf of

Basic Vegetable Products, L.P.

Communications regarding this document
should be addressed to:

Clausen Ely, Jr.
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000003

[redacted]

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I. GRAS EXEMPTION CLAIM

(i) Name of Notifier

Basic Vegetable Products, L.P., 700 Airport Drive, King City, California, 93930. All communications regarding this document should be sent to Notifier's Counsel, Clausen Ely, Jr., Covington & Burling, 1201 Pennsylvania Avenue, N.W., P.O. Box 7566, Washington, D.C. 20044-7566.

(ii) Common or Usual Name

The common or usual name of the notified substance is hydrogen peroxide. This substance is also known as hydrogen dioxide and hydroperoxide.

(iii) Conditions of Use

Notifier proposes to use hydrogen peroxide in the processing of dehydrated onions to reduce the microbial load both in and on onions prior to dehydration. The hydrogen peroxide will be applied in an aqueous solution at concentrations up to 10%, prior to dehydration of the onions. Tests sensitive to 0.51 μg/g have shown that no hydrogen dioxide residues remain on the treated onions.

(iv) Basis for the GRAS Determination

The use of hydrogen peroxide described above has been shown to be GRAS through scientific procedures, as described in greater detail in the following sections.

(v) Availability of Information

The data and information that are the basis of this GRAS determination are available for review and copying by the Agency, or will be sent to the Agency upon request. As much of the data relied upon are government studies or reports, the Agency should already have this information in its files from its previous analyses of hydrogen peroxide for use in food and food-contact articles.

[redacted]

In consideration of the data and information summarized or provided in this document, Notifier submits that the described use of hydrogen peroxide in the processing of dehydrated onions is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the Act) because such use is generally recognized as safe (GRAS).

Respectfully submitted,

BASIC VEGETABLE PRODUCTS, L.P.

By: _____
Clausen Ely, Jr.
Covington & Burling

Counsel for Basic Vegetable Products, L.P.

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[redacted]

II. DESCRIPTION OF SUBSTANCE

A. Common or Usual Name

The common or usual name for the substance that is the subject of this GRAS notification is hydrogen peroxide. This substance is also known as hydrogen dioxide and hydroperoxide.

B. Chemical Name

The chemical name for the substance that is the subject of this GRAS notification is hydrogen peroxide.

C. CAS Registry Number

The Chemical Abstracts Service Registry Number ("CASRN") for hydrogen peroxide is 7722-84-1.

D. Empirical Formula

The empirical formula for hydrogen peroxide is H_2O_2.

E. Structural Formula

The structural formula for hydrogen peroxide is H-O-O-H.

F. Molecular Weight

The molecular weight of hydrogen peroxide is 34.02.

G. Manufacturing Process

Although the more traditional process for producing hydrogen peroxide has been the electrolysis of aqueous solutions of $KHSO_4$, H_2SO_4, or NH_4HSO_4 (Considine 1995), all hydrogen peroxide manufacturing facilities constructed in the U.S. since 1957 have been based on the autoxidation of an anthraquinone (Grayson 1982).

H. Characteristic Properties

1. Physical Properties

According to Hall and Rumack (1998), the physical properties of pure, anhydrous (90 percent) hydrogen peroxide are as follows:

- Appearance: Viscous, colorless liquid.
- Melting point: -0.43°C.
- Boiling point: 152°C.
- Density: 1.463 g/cm^3.

2. Chemical Properties

The highly reactive hydrogen peroxide molecule readily participates in oxidation, epoxidation, and hydroxylation reactions, and is frequently used as an intermediate in chemical syntheses. Hydrogen peroxide is soluble in water in all proportions, soluble in alcohol and ether, but is not soluble in hydrocarbons (Considine 1995).

I. Product Specifications

1. General Specifications

The hydrogen peroxide, which is obtained from a supplier, is designated "food grade" and is guaranteed to meet "Food Chemicals Codex" specifications. Hydrogen peroxide is supplied to BVP as a 50 percent aqueous solution. This solution is diluted on-site at BVP to the appropriate concentration (i.e., 5 to 10 percent) prior to being used in processing dehydrated onions. The general specifications for food-grade hydrogen peroxide used by BVP are as follows:

- Color (APHA): 10.00 AC (maximum).
- Stability (3 hour): 99.60 percent (minimum).

2. Composition

The 50 percent hydrogen peroxide solution has an assay specification of 50.00 to 50.80 percent.

3. Purity

The supplier established the following upper limits on impurities for its food-grade hydrogen peroxide:

- Acidity (as H_2SO_4): 300.00 ppm
- Arsenic (as As): < 0.5 ppm
- Heavy metals (as Pb): < 0.5 ppm
- Iron: 0.35 ppm
- Phosphate: 35.00 ppm
- Tin: 7.00 ppm
- Residue on evaporation: 42.00 ppm

These purity limits meet or exceed those established for hydrogen peroxide by Food Chemicals Codex.

III. POTENTIAL EXPOSURE TO HYDROGEN PEROXIDE FROM PROPOSED USE

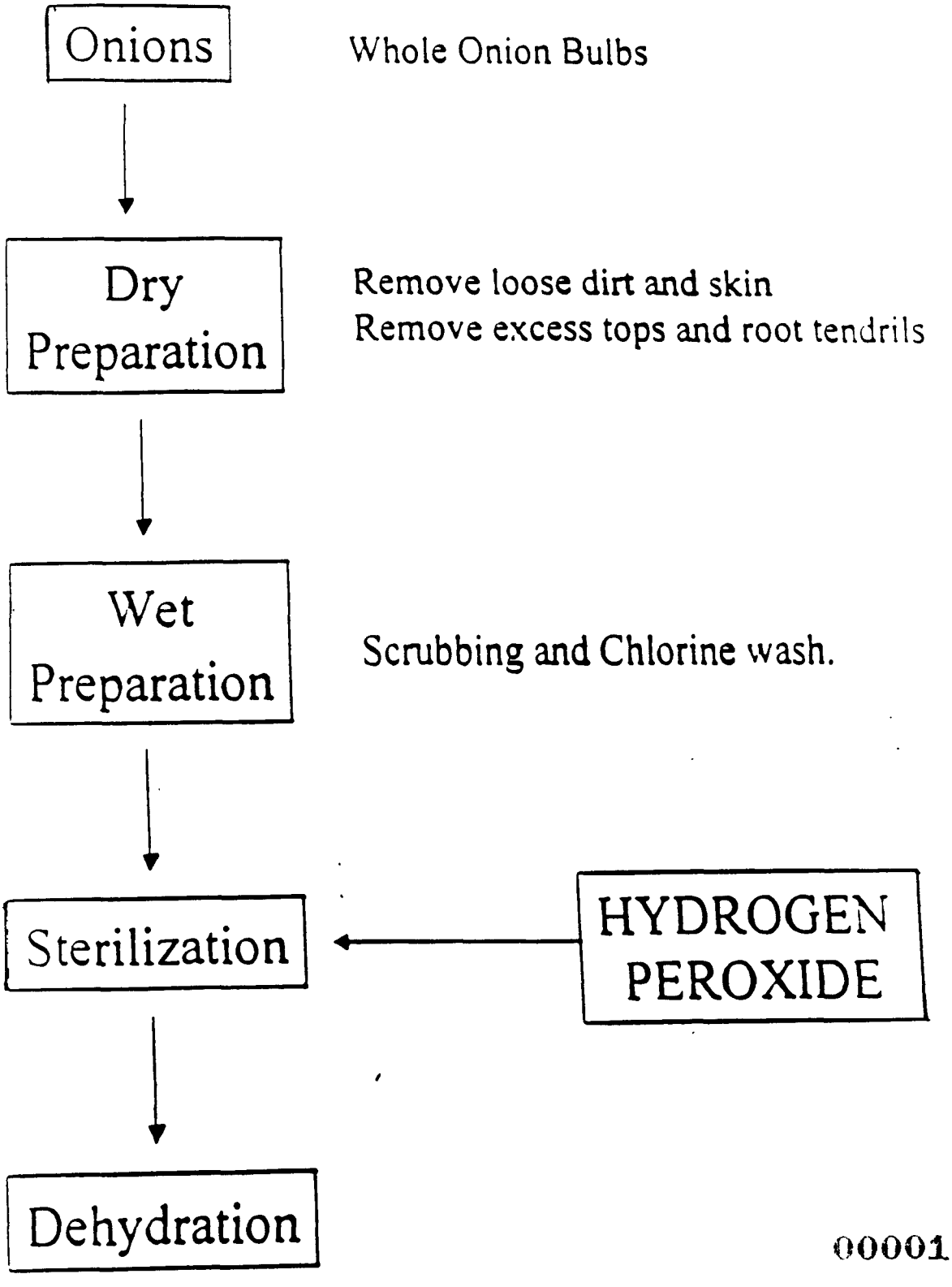
A. Description of Proposed Use

Basic Vegetable Products proposes to use hydrogen peroxide in the processing of dehydrated onions to reduce the microbial load both in and on onions prior to dehydration. The drying process moves large quantities of heated air over the onions, which acts to reduce any residual hydrogen peroxide to oxygen and water. Consequently, in line with the President's Food Safety Initiative, BVP's process can serve to increase the safety of the U.S. food supply by reducing the exposure to microorganisms from these vegetables without a significant increase in exposure to chemical residues.

Figure 1 contains a simple flow diagram of BVP's basic onion dehydration process, including the proposed hydrogen peroxide sterilization step. The first step in the process is to remove loose dirt, skin, excess tops, and root tendrils from the whole onion bulbs that enter the BVP processing facility. This step is called "dry preparation." The next step in the process ("wet preparation") is to scrub the onion bulbs with a chlorine solution. The third step ("sterilization") is where the hydrogen peroxide is applied as a 5 or 10 percent solution. The last step is the "dehydration" step where large volumes of heated air are passed over the onions to

reduce their final moisture content to around 3 to 4 percent. This last step also serves to remove any residual hydrogen peroxide.

FIGURE 1: Schematic of Basic Vegetable Products' Dehydrated Onion Production Process



B. Exposure From Proposed Use

Basic Vegetable Products retained The National Food Laboratory, Inc. ("NFL") (Dublin, CA) to measure hydrogen peroxide residues in samples of dehydrated onions treated with a 10% aqueous solution of hydrogen peroxide during processing. The NFL measured hydrogen peroxide residues in BVP onion samples employing the method of Mottola et al. (1970). The results showed that no hydrogen peroxide residues were detectable in any of the dehydrated onion samples. The final NFL reports regarding these analyses are contained in Appendix I.

As shown in the NFL report dated September 23, 1998, none of the treated samples analyzed exhibited detectable levels of hydrogen peroxide. In a subsequent report, dated October 28, 1998, the detection limit of the analytical method was determined from the average response of five "blank" samples. The limit of detection ("LOD") was defined as being three standard deviations above the average blank signal. This definition is consistent with FDA guidance (FDA 1995). Based on this definition, the LOD was determined to be 0.51 μg of hydrogen peroxide per gram of onion (0.51 μg/g). It can be concluded from this experiment that any hydrogen peroxide residue, if present, reacts with the dehydrated onion, and is completely degraded and undetectable. This conclusion is consistent with the highly reactive nature of hydrogen peroxide, especially in the presence of any organic material.

C. Exposure From Other Uses

A number of existing food-related uses currently exist in FDA's food additive regulations. These uses could potentially contribute to the EDI for hydrogen peroxide. 21 C.F.R. § 184.1366 ("Hydrogen peroxide") lists several uses for hydrogen peroxide with food. This section requires, however, that any residual hydrogen peroxide must be removed by appropriate physical and chemical means during the processing of food where it has been used. This requirement, in combination with hydrogen peroxide's highly reactive nature, dictates that exposure to residual hydrogen peroxide from these uses, if any, should be negligible. Hydrogen peroxide is also listed in 21 C.F.R. § 173.315 ("Chemicals used in washing or to assist in the peeling of fruits and vegetables"), limited to use in combination with acetic acid on fruits and vegetables that are not raw agricultural commodities. This use must be followed by a potable water rinse to remove residues of hydrogen peroxide. Again, this requirement ensures that any potential exposure to

hydrogen peroxide from this use would be insignificant. Hydrogen peroxide is also listed in 21 C.F.R. Part 178, Subpart B ("Substances utilized to control the growth of microorganisms"). The regulations in this Subpart provide for the use of hydrogen peroxide and hydrogen peroxide solutions on food-contact surfaces. Again, due to the high reactivity of hydrogen peroxide, potential exposure to humans from this use, if any, should be negligible.

Hydrogen peroxide is also approved for pesticidal use as an antimicrobial agent on fruits, tree nuts, cereal grains, herbs and spices. 40 C.F.R. § 180.1197 (63 *Fed. Reg.* 24963 (May 6, 1998)). This use also could be a source of hydrogen peroxide exposure, but for the fact that in approving hydrogen peroxide for this use, EPA noted that no hydrogen peroxide residues would be expected to enter the food supply due to its highly reactive nature. Accordingly, these other approved uses of hydrogen peroxide are not anticipated to contribute significantly to the EDI for hydrogen peroxide derived in the next section.

D. Hydrogen Peroxide EDI

Section 409(c)(5) of the Act requires that, in evaluating the safety of the proposed use of a food additive, FDA consider the probable consumption of the substance and of any substance formed in or on food because of its use, as well as the cumulative effect of the substance in the diet, taking into account any chemically- or pharmacologically-related substance or substances in such diet. Consequently, a scientific procedures GRAS determination must consider the probable consumption and cumulative effect of the substance in the diet, because a scientific procedures GRAS determination requires the same quantity and quality of evidence as is required to obtain approval of the substance as a food additive. 62 *Fed. Reg.* 18942.

Two factors are required for estimating exposure to a food substance; the daily intake of the foods in which the substance is used or can be found, and the concentration or use level of the substance in each food.

To derive food intake estimates, data from food consumption surveys are often employed. The Agency is usually interested in evaluating exposures to components of foods for those individuals who are considered "typical" (50th percentile) consumers, and those individuals who are considered "heavy" (90th percentile) consumers of the foods of interest.

Accordingly, on behalf of BVP, ENVIRON generated both 50th and 90th percentile estimates of dehydrated onion intake using TAS-Diet® software.[1] These intake estimates are based on the 1994-96 USDA CSFII data, and are for all individuals in the U.S. 6 years and older. Based on this data, ENVIRON's estimate of 50th percentile dehydrated onion intake is 1.15 g/day, while its estimate of 90th percentile dehydrated onion intake is 4.37 g/day. These estimates of dehydrated onion intake are likely to be exaggerated because they include ingestion from both the direct use of dehydrated onions and uses for which dehydrated onions are substituted for raw onions. For the substituted uses, raw onion weights were converted to the equivalent dehydrated onion weight (based on moisture content) prior to generating the estimates.

The second step in deriving an EDI for hydrogen peroxide is to multiply the above intake estimates by the hydrogen peroxide residue levels in the final product, as determined in the testing described above. Hydrogen peroxide residue levels in the final product were observed to be below the LOD. Based on these results, BVP conservatively assumed that hydrogen peroxide residue levels in dehydrated onions are present at the LOD (0.51 μg/g). Multiplying the intake estimates derived above times 0.51 μg/g yields an EDI for hydrogen peroxide of 0.60 μg/day for a typical consumer and 2.20 μg/day for a heavy consumer of dehydrated onions.

The conservative nature of this EDI must be emphasized. First, as indicated above, dehydrated onion intakes are likely to be overestimated because these intake estimates assume that dehydrated onion consumption results from the intake of dehydrated onions directly, as well as assuming that dried onions are substituted for raw onions. The potential magnitude of this overestimate can be seen in comparing the 50th percentile intake of dried onions only in individuals 6 years and older (0.18 g/day) with the 50th percentile intake of all onions (dried and

[1] Using TAS-DIET® software and data from national food consumption surveys, such as the U.S. Department of Agriculture ("USDA") Nationwide Food Consumption Survey ("NFCS") and the continuing Survey of Food Intakes by Individuals ("CSFII"), as well as the National Health and Nutrition Examination Survey ("NHANES"), and commercially sponsored surveys such as the Market Research Corporation of American ("MRCA") Menu Census and the National Purchase Diary ("NPD") Eating Trends surveys. ENVIRON provides assessments of the consumption of foods, nutrients, ingredients, additives and other food components by population categories based on age, sex, race, income or ethnic group. According to ENVIRON, the TAS-DIET® software is used by all U.S. food regulatory agencies and by multi-national corporations for analyses of the food and dietary habits of populations throughout the world.

fresh) in this same group (1.15 g/day), a greater than six-fold difference. Secondly, it was assumed that hydrogen peroxide residue levels in the final product are present at the LOD, when in fact these residue levels may be zero, especially given the highly reactive nature of hydrogen peroxide. Thus, actual exposure to hydrogen peroxide from this use is likely to be much lower.

IV. SAFETY DATA

As part of its analysis of hydrogen peroxide, BVP requested ENVIRON to review the existing safety data on hydrogen peroxide that may be relevant for this GRAS determination. Below is a summary of the most apposite studies cited by ENVIRON.

A. Toxicity of Hydrogen Peroxide

1. Human Data

Information on the toxicity of hydrogen peroxide in humans was taken from the report of the Federation of American Societies for Experimental Biology (FASEB) Select Committee on GRAS Substances Report *Evaluation of the Health Aspects of Hydrogen Peroxide as a Food Ingredient* (FASEB 1979), which evaluated the health aspects of hydrogen peroxide as a food ingredient. Data regarding the toxicity of hydrogen peroxide in humans is limited to acute incidents resulting from accidental poisonings via ingestion and is therefore not directly relevant to exposure from the proposed use of hydrogen peroxide. For completeness, however, we briefly summarize this data. Several cases of accidental poisoning in man have been described in the published literature including death by respiratory failure of a one-year-old infant within one hour after ingesting an unknown quantity of concentrated hydrogen peroxide solution (Giusti 1973). Five non-fatal poisonings were reported in persons who had consumed 25 to 100 ml of 30 percent hydrogen peroxide (Budagovskiya et al. 1971). These victims experienced sharp pains in the abdomen and behind the sternum, foaming from the mouth, vomiting, fleeting loss of consciousness, transitory motor and sensory impairment, rise in temperature, microhemorrhaging in the skin and conjunctiva, and a moderate leukocytosis. One victim, who had swallowed 100 ml of the 30 percent hydrogen peroxide solution, displayed marked visual and neurological symptoms for several days which the authors attributed to oxygen microembolisms.

2. Animal Data

The following is a brief summary of the most relevant data on the acute, subchronic, chronic, reproductive/developmental, carcinogenic, and mutagenic effects of hydrogen peroxide in mammalian test animals. The sources of this information include:

- the EPA's recent (May 6, 1998) final rule exempting hydrogen peroxide from a tolerance when used as an antimicrobial agent on fruits, vegetables, tree nuts, cereal grains, herbs, and spices (63 *Fed. Reg.* 24955);
- the Select Committee's report, *Evaluation of the Health Aspects of Hydrogen Peroxide as a Food Ingredient* (FASEB 1979);
- the EPA's 1993 document, *Reregistration Eligibility Decision ("RED") for Peroxy Compounds* (EPA 1993); and
- the International Agency for Research on Cancer ("IARC") Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Allyl Compounds, Aldehydes, Epoxides, and Peroxides (IARC 1985).

If possible, the citation from the primary literature has been provided for each of the toxicity studies summarized below. However, in all cases, ENVIRON relied strictly on the summaries of the toxicity studies found in the secondary sources listed above in conducting this toxicological review.

These animal data show that significant toxicological effects of hydrogen peroxide in mammalian test systems are measurable only at high doses, and are primarily the result of the corrosive and irritating nature of hydrogen peroxide. Moreover, any chronic effects observed are also a consequence of hydrogen peroxide's corrosivity. Hydrogen peroxide doses high enough to be of toxicological concern are not expected under food-contact use due to the rapid decomposition of hydrogen peroxide into oxygen and water.

a. Acute Toxicity Studies

The acute toxicity data on hydrogen peroxide were taken from the *RED for Peroxy Compounds* (EPA 1993). These data are as follows:

- Acute oral LD_{50} (mice) 2,000 mg/kg.
- Acute dermal LD_{50} (rats) 4,060 mg/kg.
- Acute inhalation LC_{50} (mice) 227 µl/L.
- Eye irritation (rabbits) Severe irritation
- Dermal irritation (rabbits) Corrosive

Based on the results of these studies, EPA concluded that hydrogen peroxide (as well as other peroxy compounds) is corrosive and severely irritating to the eyes, skin, and mucous membranes, but possesses only moderately low oral toxicity.

b. Subchronic Toxicity Studies

A group of weanling Osborne-Mendel male rats were administered 0.45 percent hydrogen peroxide (about 560 mg/kg/day) *ad libitum* in drinking water for 3 weeks (Hankin 1958). These rats were compared with controls who received tap water over the same period. Both fluid intake and weight gain in the hydrogen peroxide group were significantly less than controls. However, when corrected for differences observed in water intake between control and treated rats, there were no significant differences observed in absolute and relative body weights and organ weights of the kidney, spleen, heart, or testes. A no-observed-effect level ("NOEL") for hydrogen peroxide of 560 mg/kg/day was established from this study.

In a similar experiment, young male Holtzman rats were administered 0, 0.5 (500 mg/kg/day), 1.0 (1,000 mg/kg/day), or 1.5 (1,500 mg/kg/day) percent hydrogen peroxide in their drinking water for 8 weeks (Shapiro et al. 1960). Growth was significantly retarded in all groups receiving hydrogen peroxide, and this retardation was proportional to hydrogen peroxide concentration. Increased mortality was noted at the highest dose (1,500 mg/kg/day). Increased incidence of dental caries and pathological changes in the periodontium were also noted in the mid- and high-dose groups. A LOEL for hydrogen peroxide of 500 mg/kg/day was established from this study, but a NOEL was not.

Male and female C57BL/6N, DBA/2N, and BALB/cAnN mice were administered 0, 0.1, or 0.4 percent hydrogen peroxide in drinking water for 30 or 60 days (Ito et al. 1981). Equivalent hydrogen peroxide doses (assuming a water intake of 150 ml/kg/day) were 0, 150, or 600 mg/kg/day. The high dose (600 mg/kg/day) resulted in erosion of the glandular stomach in 29 percent of mice treated for 30 days and in 40 percent of mice treated for 60 days. Duodenal

lesions, but no frank nodules, were also observed at the high dose. A LOEL of 600 mg/kg/day was established, but due to the lack of data reported at the 150 mg/kg/day dose, a NOEL could not be definitively assigned.

c. Chronic Toxicity Studies

Wistar rats were administered 30 or 60 mg/kg/day hydrogen peroxide for 100 days by gastric intubation (Kawasaki et al. 1969). The high-dose group (60 mg/kg/day) exhibited significantly decreased growth rates after 20 days. After 100 days, this same group showed decreases in plasma protein, hematocrit, and plasma catalase activity. Administration of these same hydrogen peroxide dose levels in feed had no effects. A NOEL for hydrogen peroxide of 30 mg/kg/day was established from this study.

Romanowski et al. (1960) administered hydrogen peroxide to rats in their drinking water at concentrations ranging from 0.25 to 10 percent for 146 days. All animals receiving hydrogen peroxide concentrations of 2.5 percent or higher died within 43 days. Nine of 10 rats administered 0.25 percent hydrogen peroxide (about 250 mg/kg/day) and 8 of 10 rats administered 0.50 percent hydrogen peroxide (about 500 mg/kg/day) survived the test period. However, the weight gain in each of these groups was less than that of the controls.

Three-week-old mice (strain not specified) were administered 0.15 percent hydrogen peroxide *ad libitum* in their drinking water for 35 weeks, equivalent to a hydrogen peroxide dose of about 150 mg/kg/day (Aoki and Tani 1972). These mice grew normally and developed no visible abnormalities during the test period. Upon necropsy, degenerative changes in the liver and kidney, as well as inflammation, irregularity and slight necrosis of the stomach wall, were observed. In addition, the lymphatic tissue of the wall of the small intestine was hypertrophic. The LOEL in this study was determined to be 150 mg/kg/day, but a NOEL was not established.

Male and female C57BL/6N mice were administered 0, 0.1, or 0.4 percent hydrogen peroxide in their drinking water for up to 700 days (Ito et al. 1981). Hydrogen peroxide doses of 0, 150, and 600 mg/kg/day were estimated based on an assumed water intake of 150 ml/kg/day. The gastrointestinal tract was examined over the course of the study through serial sacrifices at time points between 90 and 700 days. Gastric lesions consisting of erosion and hyperplastic

nodules were detected in the stomach and duodenum after 1 to 2 years of exposure. A LOEL of 150 mg/kg/day was established from this study.

d. Reproductive/Developmental Toxicity Studies

Two older studies on the developmental and reproductive effects of hydrogen peroxide are available. As part of the Hankin (1958) study summarized above, 3 female rats receiving 0.45 percent hydrogen peroxide (about 500 mg/kg/day) in drinking water for five months were mated with normal males. Normal litters were produced. The male rats from these litters were then given 0.45 percent hydrogen peroxide in drinking water for 9 months. The only noticeable difference between these rats and male littermates receiving tap water was decreased weight gain in the hydrogen peroxide group.

In the second study (Mann and Leone 1953), three-month-old male albino mice were administered 0.33 (about 330 mg/kg/day) and 1.0 (about 1,000 mg/kg/day) percent hydrogen peroxide in their drinking water for 7 to 28 days before mating them with normal females. All females became pregnant within a few days and in each case, healthy offspring were born in litters of normal size.

These data indicate no apparent developmental or reproductive effects observed from administration of hydrogen peroxide at concentrations up to 1 percent (1,000 mg/kg/day).

e. Carcinogenicity Studies

Gastric carcinogenesis was investigated in male Wistar rats. Twenty-one rats received the initiator MNNG in drinking water for 8 weeks at 100 mg/L, while uninitiated rats (10 animals) received plain drinking water. After 8 weeks, both groups received 1 percent hydrogen peroxide in drinking water from Week 8 through Week 40. Two other groups (30 and 10 rats, respectively) were chosen as initiated and uninitiated controls. Surviving rats were sacrificed and necropsied at 40 weeks. Erosion and ulceration along the limiting ridge of the fundic mucosa were observed. Initiated rats showed an increased incidence of adenomatous hyperplasia in this region of the stomach. There were no adenocarcinomas induced in the stomach or duodenum. Papillomas of the forestomach were induced by hydrogen peroxide alone.

Three-month-old Syrian hamsters were administered: (1) twice weekly applications of a 30 percent hydrogen peroxide solution in the left buccal pouch; or (2) twice weekly buccal applications of 0.25 percent 9,10 dimethyl-1,2-benz-anthracene ("DMBA") combined with either 30 percent or 3 percent hydrogen peroxide (hydrogen peroxide applied on a different day than the DMBA); or (3) DMBA only. Buccal pouches were examined for tumor development at 19 and 22 weeks after sacrifice. No epidermoid carcinomas were observed after 22 weeks of treatment with hydrogen peroxide alone. All three groups receiving DMBA treatment did develop tumors. The tumors in the group receiving the 30 percent hydrogen peroxide and DMBA were reported to be more anaplastic with deeper penetration of tissue. It was concluded that hydrogen peroxide may augment oral carcinogenesis induced by DMBA.

Male and female weanling C57BL/6J mice were administered 0, 0.1, or 0.4 percent hydrogen peroxide in drinking water for up to 108 weeks (Ito et al. 1981). Erosion of the glandular stomach was observed in 20 percent and 42 percent of mice at the 0.1 percent and 0.4 percent dose levels, respectively, compared to 4 percent in controls. Duodenal nodules were observed in treated mice and were classified as hyperplasias, adenomas, or carcinomas. Hyperplasia was significantly increased at the 0.1 percent and 0.4 percent dose levels (40 percent and 62 percent of treated mice, respectively), as was the incidence of duodenal carcinoma, observed in 5 of 99 high-dose animals, 1 of 101 low-dose animals, and absent in controls.

Various strains of mice (C57Bl/6N, DBA/2N, BALB/c) were exposed to 0.4 percent hydrogen peroxide in drinking water over their lifetime (Ito et al. 1982). Appearance of duodenal lesions (plaques and nodules) was noted in all strains after 90 days of treatment. Temporary withdrawal of hydrogen peroxide produced apparent reversibility in C57BL/6N mice only after 30 days of no treatment. After 150 days of treatment, C57BL/6N mice appeared to have an increased incidence of duodenal lesions relative to the other two strains. After 420 to 740 days of treatment, the incidence of duodenal carcinoma was 0, 1 percent, and 5 percent in control, low dose, and high dose, respectively. This study did not present concurrent control data, and used varying numbers of mice for examination at the various time points. Therefore, results from this study are considered equivocal.

Strains of mice differing in catalase activities of the duodenum, blood, and liver (in order of decreasing activity: C3H/HeN, B6C3F1, C57BL/6N, C3H/C) were administered 0.4 percent hydrogen peroxide in their drinking water for approximately 6 months (Ito et al. 1984). The duodenum in each strain was examined for both the incidence of lesions and total lesions. Approximately 18 to 22 mice per strain were examined. The data suggested that the number of duodenal lesions per mouse and total incidence of duodenal lesions was inversely correlated with catalase activity.

Recent experimental evidence (Upham et al. 1997) has implicated hydrogen peroxide in the inhibition of gap junctional intercellular communication in rat liver epithelial cells (a significant step in production of tumors). These recent data lend support to the above studies implicating high levels of hydrogen peroxide as a promotor of tumorigenesis. However, IARC has designated hydrogen peroxide as not classifiable as to carcinogenicity, based on the data noted above (IARC 1985).

3. Genotoxicity Data

In a standard plate incorporation assay, hydrogen peroxide (concentrations not stated) was weakly mutagenic to strains TA98, TA97, and TA1537 for frame shift mutations and to strain TA102 for oxidative mutations, but was not mutagenic to strains TA100 and TA1538.

Using isolated hepatocytes from female Fischer rats, hydrogen peroxide was incubated at concentrations ranging from 0.01 to 1 mM for 1 hour at 37°C. Overt cytotoxicity was observed at 1 mM. A concentration-dependent increase in single-strand DNA breaks was observed at all other exposure levels. No double-strand DNA breaks or DNA cross-links were observed.

In a human bronchial epithelial cell system, nucleic acid synthesis was observed to be significantly decreased after exposure to hydrogen peroxide at 1.2 mM for six hours followed by a cell growth period of 7 to 9 days. At 100 mM, single-strand DNA breaks and DNA-protein cross-links were observed, with single-strand breaks predominating. DNA strand breakage has also been observed in other test systems (e.g., hamster V79 cells and bovine pulmonary artery and aortic endothelial cells).

Cell killing and DNA damage were examined in Chinese hamster fibroblast cells (V79-379A). After incubation of cells with 1 to 100 mM hydrogen peroxide at ice-cold temperatures for 10 or 20 minutes, single-strand breaks were observed at 1 mM hydrogen peroxide. Double-strand breaks and cell killing were observed at higher (10 mM) concentrations of hydrogen peroxide.

4. Conclusions

At the end of its evaluation of the health aspects of hydrogen peroxide as a food ingredient (FASEB 1979), the Select Committee concluded that the toxic effects of hydrogen peroxide in animals by all routes studied occurred only at levels several orders of magnitude greater than man's possible exposure from food sources or packaging materials. In addition, these toxic effects are either directly or indirectly associated with hydrogen peroxide's corrosive and irritating nature. Furthermore, the Select Committee also stated that there is no evidence that hydrogen peroxide is carcinogenic, teratogenic, or mutagenic at levels present in foods treated with hydrogen peroxide during processing. The subsequent studies on hydrogen peroxide have supported these conclusions. FDA has affirmed as GRAS the use of hydrogen peroxide in other food and food-contact uses (21 C.F.R. § 184.1366), and EPA recently granted an exemption from the requirement of a tolerance for hydrogen peroxide residues on certain foods. (40 C.F.R. § 189.1197, 63 *Fed. Reg.* 24963).

B. Secondary Toxic Effects of Hydrogen Peroxide

In evaluating the human health impacts of hydrogen peroxide use, one must consider not only its intrinsic toxicity, but also any secondary deleterious effects which may result from its addition to food. In particular, one must evaluate: (1) the possible destruction of essential nutrients, and (2) the production of potentially toxic reaction products. Both of these factors were discussed by the Select Committee in their report (FASEB 1979).

1. Destruction of Essential Nutrients

In evaluating the health aspects of hydrogen peroxide as a food ingredient, the Select Committee reviewed the available studies that examined whether hydrogen peroxide treatment during processing resulted in nutritional changes in the final product (FASEB 1979). The Select

Committee concluded that vigorous treatment of foods with hydrogen peroxide may cause some destruction of ascorbic acid (vitamin C), methionine, and cystine. However, the Select Committee also believes that, under conditions normally employed, the loss of these nutrients is nutritionally insignificant. Furthermore, dehydrated onions do not contain particularly high levels of any of these three nutrients (i.e., ascorbic acid, methionine, and cystine). Thus, the impact of hydrogen peroxide treatment on the nutritional content of dehydrated onions would be expected to be particularly insignificant.

To ensure that the use of hydrogen peroxide as a processing aid in the production of dehydrated onions does not significantly alter the nutrient profile of the finished product, BVP retained Lancaster Laboratories (Lancaster, PA) to characterize the nutrient content of both hydrogen peroxide-treated (10% aqueous hydrogen peroxide solution) and untreated dehydrated onions. The resulting nutrient profiles were then compared. This comparison is displayed in Table 1, and is based on the analysis reports in Appendix II. Table 1 includes the most commonly measured nutritional parameters for food labeling (i.e., calories, carbohydrate, protein, and fat), as well as selected vitamins (i.e., thiamin, riboflavin, vitamin C, and vitamin B_6). These particular vitamins were chosen because they are believed to be the most susceptible to a strong oxidizing agent such as hydrogen peroxide. Table 1 shows that for the nutritional parameters and selected vitamins included in the nutrient profile, the only difference is that the mean level of vitamin C in the hydrogen peroxide-treated onions is approximately 50 percent lower than the mean level of vitamin C in the untreated onions (9.33 versus 20 mg/100 g, respectively). However, onions are not a particularly good source of vitamin C, as evidenced by the following:

- Multiplying the mean level of vitamin C in untreated dehydrated onions (20 mg/100 g) times the 90th percentile intake of dehydrated onions (4.37 g/day)[2] yields an estimated vitamin C intake from dehydrated onion consumption of about 0.9 mg/day. The recommended daily allowance ("RDA") for vitamin C is 60 mg/day (NRC 1989). This estimated vitamin C intake for "heavy" consumers of dehydrated onions is only 1.5 percent of the RDA.

[2] See Chapter III.D for a description of how this intake value was estimated.

- The vitamin C content of onions (on a wet weight basis) is 6.4 mg/100 g, while the vitamin C content of some other fruits and vegetables is as follows: green peppers - 89.3 mg/100 g; broccoli - 74.6 mg/100 g; strawberries - 56.7 mg/100 g; and oranges - 53.2 mg/100 g (USDA 1998).

Therefore, this reduction in vitamin C (although relatively large on a percentage basis) is not of any nutritional significance.

TABLE 1: Comparison of Nutrient Profiles of Hydrogen Peroxide-Treated and Untreated Dehydrated Onion Samples

TABLE 1
Comparison of Nutrient Profiles of Hydrogen Peroxide-Treated and Untreated Dehydrated Onion Samples

Nutritional Parameter	**Dehydrated Onions Processed with Hydrogen Peroxide (Mean ± SD)[1]**	**Dehydrated Onions Processed Without Hydrogen Peroxide (Mean ± SD)[1]**
Moisture	3.69 (± 0.02) %	3.69 (± 0.06) %
Carbohydrate	79.5 (± 0.06) %	79.1 (± 0.31) %
Protein[2]	11.6 (± 0.10) %	11.6 (± 0.15) %
Fat	1.23 (± 0.12) %	1.27 (± 0.38) %
Ash	3.98 (± 0.02) %	4.26 (± 0.04) %
Caloric Value[3]	375.3 (± 0.58) Cal/100 g	374.7 (± 2.08) Cal/100 g
Selected Vitamins[4]		
Thiamin	0.49 (± 0.03) mg/100 g	0.49 (± 0.01) mg/100 g
Riboflavin	0.28 (± 0.03) mg/100 g	0.26 (± 0.05) mg/100 g
Vitamin C (ascorbic acid)	9.33 (± 0.58) mg/100 g	20 (± 1.0) mg/100 g
Vitamin B_6 (as pyridoxine)	1.3 (± 0.0) mg/100 g	1.3 (± 0.1) mg/100 g

[1] The descriptive statistics are based on analysis results from three dehydrated onion samples.
[2] The percent protein was calculated from percent nitrogen using a factor of 6.25.
[3] Caloric value was estimated based on the following formula:
Calories/100 g = 4(% protein) + 9(% fat) + 4(% carbohydrate).
[4] Vitamins were selected based on their predicted sensitivity to oxidation.

2. Production of Potentially Toxic Reaction Products

In exploring the possible adverse consequences of treating foods with hydrogen peroxide, one must also consider the possible formation of toxic oxidation products. As an oxidizing agent, hydrogen peroxide theoretically can form a number of reaction products with food constituents, whose nature and significance are largely speculative. Of special concern are the unsaturated fatty acids and the sterols that may be present in the treated foods. Both groups of compounds are vulnerable to oxidation and may yield products with putative carcinogenic or other toxic properties.

Based on its review of the potential toxic effects of the oxidation products of lipids, carbohydrates, and proteins resulting from hydrogen peroxide use, the Select Committee (FASEB 1979) concluded:

> Various oxidation products of normal food constituents are formed by the action of hydrogen peroxide. It is possible that such products might include epoxides or peroxides of unsaturated fatty acids and sterols, some of which are suspected of being carcinogenic or atherogenic under specialized conditions. However, none of the oxidation products thus far tested has proved carcinogenic when given by mouth, even at levels many times greater than any reasonable intake in food. Angiotoxicity has been produced only with amounts of sterol oxidation products several orders of magnitude greater than would be produced under conditions currently practiced. There is no evidence that such products are, in fact, produced under current conditions of hydrogen peroxide usage. Because of the vulnerability of epoxides and peroxides to gastrointestinal action, only a small fraction of the amount ingested would be absorbed and this in turn would be subjected to hydrolysis by liver enzymes.

Furthermore, the lipid content of onions is relatively low, as evidenced by the fat content of the BVP dehydrated onion samples (1 to 2 percent). Thus, the oxidation of unsaturated fatty acids would be expected to be even less of a concern when using hydrogen peroxide in the processing of dehydrated onions. However, to ensure that such oxidation products are not formed as a result of hydrogen peroxide treatment during dehydrated onion processing, BVP retained Lancaster Laboratories to conduct a 2-thiobarbituric acid ("TBA") assay, a representative measure of lipid oxidation, on both untreated and hydrogen peroxide-treated onion

samples. The results of this assay showed that in the untreated onion samples, TBA values averaged 0.29 (± 0.07) meq/kg, while in the onion samples treated with a 10% aqueous hydrogen peroxide solution, TBA values averaged 0.67 (± 0.11) meq/kg. Although TBA values were higher in the treated onion samples, the TBA values in both groups of onion samples were very low, and not that much higher than the limit of quantitation ("LOQ") of the assay (0.1 meq/kg). Therefore, the amount of lipid oxidation represented by these TBA values is insignificant, and thus not of particular toxicological concern. These TBA results are based on the Lancaster Laboratories analysis reports in Appendix II.

C. Sufficiency of Safety Data

As stated in FDA's "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food," ("Redbook II," 1993), the extent and type of toxicity testing recommended for additives used in food depends on the initial "Concern Level" to which that additive has been assigned and available information about the metabolism, chemical composition, and toxicity of the additive. Recommendations for minimum testing are associated with each "Concern Level." These recommendations reflect the FDA's consensus that extensive toxicity testing should be reserved for additives with high exposures and potentially reactive structures, and for additives that induce adverse toxic effects at low doses or after short exposures.

Based on the previously derived EDI of about 2.2 μg/day (or 0.04 μg/kg/day for a 60-kg person) for a heavy consumer of onions, the estimated concentration of hydrogen peroxide in the daily diet is about 0.7 ppb. According to the "Redbook II", assuming hydrogen peroxide is a "Structure Category C" compound (substances whose chemical structures suggest that they have the greatest potential for toxicity), hydrogen peroxide would be classified as a "Concern Level I" substance (i.e., daily exposure $\leq$ 0.62 μg/kgbw or 12.4 ppb in the diet).

Toxicity tests recommended for a Concern Level I substance are as follows:

- short-term tests for genetic toxicity; and
- a short-term feeding study (at least 28 days in duration) in a rodent species, which includes an evaluation of the potential neurotoxicity and immunotoxicity of the test substance.

Clearly, the existing toxicity data on hydrogen peroxide exceed that recommended for a "Concern Level I" substance.

V. GRAS DETERMINATION

A. Safety Assessment

A scientific procedures GRAS determination requires that first, information about the substance establish that the intended use of the substance is safe. The FDA has defined "safe," under 21 C.F.R. §170.3(i), as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. This same regulation specifies that three factors must be considered in determining safety. These three factors are:

1. the probable consumption of the substance and of any substance formed in or on food because of its use;

2. the cumulative effect of the substance in the diet, taking into account any chemically- or pharmacologically-related substance or substances in such diet; and

3. safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of food and food ingredients, are generally recognized as appropriate.

The first factor is a statement of the EDI, as described above. The remaining considerations are used to establish the ADI for the substance. The ADI represents the maximum amount of the substance that can be safely consumed by humans on a daily basis for a lifetime. An ADI is usually established by application of a safety factor to the highest NOEL identified in the most sensitive animal species studied. Under 21 C.F.R. §170.22, the FDA states that, except where evidence is submitted which justifies use of a different safety factor, a safety factor of 100 to 1 is to be used in applying animal experimentation data to man, that is, tolerance for the use of a human food ingredient will not exceed 1/100th of the maximum amount demonstrated to be without harm to experimental animals. The ADI for the substance is then compared with the probable human consumption of the substance (the EDI). As long as the EDI for the substance is less than (or approximates) its ADI, the substance can be considered safe for its intended use (Redbook II, p. 12).

As previously determined in this Notification, based on testing for hydrogen peroxide residues and consumption data on dehydrated onions, the EDI for hydrogen peroxide for a heavy consumer of dehydrated onions is 2.2 μg/day from this use.

Based on the animal toxicity data on hydrogen peroxide, a NOEL for hydrogen peroxide of 30 mg/kg/day was established. This NOEL is from a subchronic/chronic (100-day) animal study where hydrogen peroxide was administered to rats via gastric intubation at doses of 30 and 60 mg/kg/day (Kawasaki et al. 1969). At the highest dose (60 mg/kg/day), decreases in growth rate, plasma protein, hematocrit, and plasma catalase activity were observed.

In deriving an ADI for a food additive, FDA's "Redbook II" states the following:

> For non-cancer endpoints, the NOEL is divided by a safety factor to obtain an estimate of the maximum acceptable daily intake (ADI) of the additive for humans. The selection of a safety factor is based on the biological significance of the endpoint, uncertainties inherent in extrapolating information about adverse effects from toxicity studies in animals to human populations, and other judgmental factors. The food additive procedural regulations (21 C.F.R. § 170.22) state that a safety factor of 100 will be used as a general rule in applying animal test data to man. However, exceptions to a safety factor of 100 are permitted in accordance with the nature and extent of data available and the circumstances of use of the food additive.

Therefore, in the case of hydrogen peroxide, application of a 100-fold safety factor to the highest NOEL identified in the most sensitive animal species studied could be used to derive an ADI for hydrogen peroxide. While safety factors of 100 have traditionally been applied by the FDA to chronic studies, larger values (up to 1,000 or more) are sometimes used for subchronic or other types of toxicological studies to compensate for the decreased duration or the specialized nature of the study (Rulis 1987). More recently, Rodricks et al. (1995) suggest that if the NOEL derives from a subchronic toxicity study, and a chronic ADI is desired, an additional factor of 10 be applied to the typical safety factor of 100.

Application of a 1,000-fold safety factor to the NOEL of 30 mg/kg/day yields an ADI for hydrogen peroxide of 0.030 mg/kg/day or 30 μg/kg/day. This ADI is equivalent to a hydrogen peroxide intake of 1,800 μg/day for a 60-kg person.

As demonstrated in Section IV, C, the existing safety data on hydrogen peroxide is more than is required by FDA to assess the safety of this substance in the diet. Therefore, evaluation of the safety of hydrogen peroxide employed as a processing aid in the production of dehydrated onions can be accomplished through a review of this data, followed by comparison of the EDI for hydrogen peroxide with its ADI. So long as the EDI is less than (or approximates) the ADI, then the proposed use may be considered safe as defined under 21 C.F.R. §170.3(i).

The ADI for hydrogen peroxide is 1,800 µg/person/day. The EDI for hydrogen peroxide, based on its intended use as a processing aid in the production of dehydrated onions, is at most 2.2 µg/person/day. Clearly, this EDI is far below the ADI, and thus hydrogen peroxide is safe for use in processing dehydrated onions under all reasonably anticipated use conditions likely to occur under GMP.

Further evidence of safety is provided by the fact that hydrogen peroxide residues in dehydrated onions processed with hydrogen peroxide are, at most, 0.51 µg/g or 0.51 ppm. This concentration is well below the exemption tolerance of 120 ppm recently established by EPA for the use of hydrogen peroxide as an antimicrobial agent on fruits, vegetables, tree nuts, cereal grains, herbs, and spices (40 C.F.R. §180.1197, 63 *Fed. Reg.* 24963 (May 6, 1998)). Further, this level is well below the 10 ppm level FDA found sufficiently low to establish the safety of hydrogen peroxide when used as an anti-microbial in milk during the cheese-making process. 46 *Fed. Reg.* 44434, 44435 (September 4, 1981).

B. General Recognition of Safety

In the previous section, the use of hydrogen peroxide as a processing aid in the production of dehydrated onions has been determined to be safe through scientific procedures. As required by 21 C.F.R. §170.30, the scientific data and information on which the safety determination of hydrogen peroxide is based are available in the published literature or are otherwise publicly available to experts qualified by training and experience to evaluate the safety of food and food additives. Accordingly, these data meet the common knowledge element required for all GRAS determinations. Additionally, both FDA and EPA have used this publicly available data to make determinations that hydrogen peroxide is safe for specific food uses. 46

Fed. Reg. 44434 (September 4, 1981); 51 *Fed. Reg.* 27169 (July 30, 1986); 63 *Fed. Reg.* 24955 (May 6, 1988).

The determination that hydrogen peroxide is safe, and GRAS, as a processing aid in the production of dehydrated onions has been made through the deliberations of Vasilios H. Frankos, Ph.D., Principal with ENVIRON Corporation, and Duncan Turnbull, D.Phil., Senior Science Advisor with ENVIRON Corporation. These individuals are qualified by scientific training and experience to evaluate the safety of foods and food additives. These qualifications are set out in Appendix III. These experts have carefully reviewed and evaluated the publicly available information summarized in this document, including the current FDA regulatory approvals of hydrogen peroxide, as well as the potential human exposure to hydrogen peroxide as a result of its proposed use, and have concluded:

> No evidence exists in the available information on hydrogen peroxide that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public health when hydrogen peroxide is employed at levels that might reasonably be expected from its proposed use as a processing aid in the production of dehydrated onions.

It is their opinion that other qualified and competent scientists reviewing the same publicly available data would reach the same scientific conclusion.

Therefore, Basic Vegetable Products considers the use of hydrogen peroxide as a processing aid in the production of dehydrated onions to be safe, and GRAS, under all reasonably anticipated use conditions likely to occur under GMP. Because hydrogen peroxide is GRAS for its intended use, it is therefore exempt from the premarket approval requirements of the Federal Food, Drug and Cosmetic Act.

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APPENDIX I

Determination of Hydrogen Peroxide Residuals in Hydrogen Peroxide-Treated Dehydrated Onion Samples - 3 Reports (The National Food Laboratory, Inc.)

The National Food Laboratory, Inc.
6363 CLARK AVENUE, DUBLIN, CALIFORNIA 94568-3097
(925) 828-1440 • Fax (925) 833-8795

September 23, 1998

Mr. Omar Houry
Basic Vegetable Products
700 Airport Drive
King city, CA 93930-2501

Reference: CM 4032

Enclosed is The NFL's report on hydrogen peroxide residues in dried onion flakes.

Please do not hesitate to contact me if you have any questions concerning this report.

Your samples will be retained for a period of thirty days from the date of this report, at which time, unless notified to the contrary, they will be discarded.

Thank you for using the services of The National Food Laboratory.

Sincerely.

Bradford Allen, Research Chemist

cc: Mary Jo Smith, Accounting

000033

FAXED
SEP 2 4 1998
BY:

Hydrogen Peroxide Residues in Dried Onions

NFL Project: CM 4032
Date: September 24, 1998

Summary
No hydrogen peroxide residues were found in the "Treated" samples. The detection limit was 0.15 ppm in the dried onion samples. There was no recovery of "added" hydrogen peroxide to the "Treated" samples.

Principle
This procedure measures hydrogen peroxide by employing the enzyme peroxidase to catalyze the oxidation of leuco crystal violet by hydrogen peroxide. The method is sensitive to 0.015 ppm.

Reference
"*Absorptiometric Determination of Hydrogen Peroxide in Submicrogram Amounts with Leuco Crystal Violet and Peroxidase as Catalyst*"; Mottola, H.A. Simpson, B.E. and Gorin, G.; Anal. Chem., 42 ,1970, pg. 410

Reagents
Horseradish Peroxidase, Type II (HRP) (Sigma Chemical Co.)
Leuco crystal violet (LCV) (Aldrich Chemical Co.)
Sodium acetate
Glacial acetic acid
Hydrochloric acid

Apparatus
Perkin Elmer Lamba II UV/VIS Spectrophotometer

Solutions

1. LCV solution – dissolve 50 mg of leuco crystal violet in 80 mL of 0.5 % hydrochloric acid and make to 100 mL volume with 0.5 % hydrochloric acid. Protect from light.

2. HRP solution – dissolve 10 mg of horseradish peroxidase in 10 mL of water. Protect from light.

3. Acetate buffer – prepare a buffer solution form equal parts of 2 M sodium acetate and 2 M acetic acid. Adjust pH to 4.5 with glacial acetic acid.

Standards

Prepare standards by diluting 35% hydrogen peroxide with water successively to achieve standard concentration in the range of 0.010 to 1.00 ug/mL.

Procedure

Blend the dried onion flakes to a powder using a blender.
Add 10 mL of distilled water to 1.0 g of sample and let sit 10 minutes.
Filter through a 0.45 membrane filter.

For standards, pipette 1 mL of each hydrogen peroxide standard into a test tube.
For samples, pipette 1 mL of filtered sample extract into test tube.
Pipette 200 uL of LCV solution each test tube.
Pipette 200 uL of HRP into each test tube.
Add 1 mL of sodium acetate buffer.
Shake to mix and immediately determine the absorbance at 596 nm.

Results

A sample identified as "Treated 9-1-98" was analyzed. The following results were obtained.

Sample	Absorbance	"Blank" Corrected Absorbance	Hydrogen Peroxide (ug/mL)	Sample Weight (g)	Final Volume (mL)	Hydrogen Peroxide (ppm)
Standard 0.90 ug/mL	0.866					
Standard 0.30	0.288					
Standard 0.12 ug/mL	0.104					
Standard 0.06 ug/mL	0.047					
Standard 0.03 ug/mL	0.017					
Standard 0.015 ug/mL	0.012					
Blank	0.014			1.0	10.0	
Blank	0.015			1.0	10.0	
Ave Blank	0.014					
Treated #1	0.012	0.000	ND	1.0	10.0	ND
Treated #2	0.015	0.001	ND	1.0	10.0	ND
Treated #3	0.018	0.003	ND	1.0	10.0	ND
Treated #4	0.011	0.000	ND	1.0	10.0	ND
Treated #5	0.016	0.002	ND	1.0	10.0	ND
Spiked 1.8 ppm	0.015	0.000	ND	1.0	10.0	ND
Spiked 1.8 ppm	0.010	0.000	ND	1.0	10.0	ND
Spiked 1.8 ppm	0.011	0.000	ND	1.0	10.0	ND

The "Sample Blank" samples were prepared by analyzing the samples in the same manner as the samples, except that no LCV was added. The spiked samples were prepared by re-hydrating 1.0 g of the dried onion samples with 10 mL of hydrogen peroxide solution (1.8 ug/mL).

The detection limit of the standards was calculated as 3X the absorbance of a "Reagent Blank". The "Reagent Blank" absorbance was 0.004 AU. The detection limit was calculated to 0.012 AU, which corresponded to a concentration of 0.015 ug/mL.

The concentration of hydrogen peroxide in the sample extracts was calculated from the regression data of the standard curve. From the regression data, a slope, y-intercept and correlation coefficient were calculated. The standard curve was linear from 0.90 ug/mL to 0.015 ug/mL. The equation for the standard curve was (-0.008736) + (0.9729245)X.
The r^2 was 0.9998.

The concentration in the samples were calculated using the following equations:

To calculate the ug/mL found in the sample extracts, use the equation
[y = mx + b] to solve for x.
x = ug/mL in extract
y = absorbance
m = slope
b = y-intercept

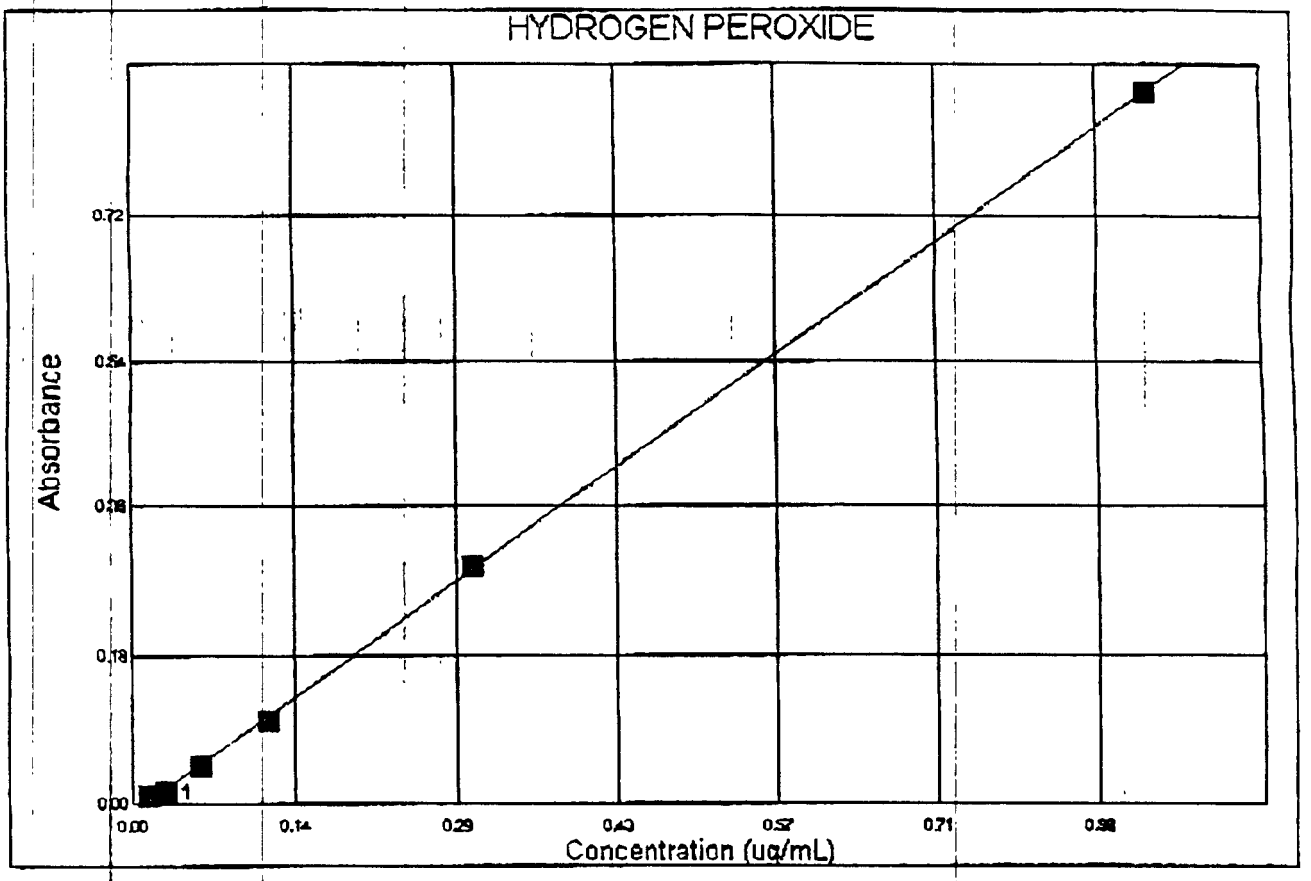
To convert to ppm in the samples, subtract out the absorbance from the "Sample Blank", multiply the ug/mL found by the final volume and divide by sample weight.

Absorbance Blank:	0.014
Absorbance Sample:	0.012
Slope:	0.9729
Y-Intercept:	-0.00874

(0.016-0.014) = (0.9729(x) + (-0.00874)
solving for x, x = 0.01 ug/mL, which is below the detection limit.

The detection limit for the samples was calculated by multiplying the concentration of the lowest detectable standard and diving by the sample weight.

DL = 0.015 ug/mL X 10 mL / 1.0 g = 0.15 ug/g



Curve Parameters:

First Order Polynimail Fit
r^2 = 0.999823
Calibration Curve = (-0.008736) + (0.972924)X

The National Food Laboratory, Inc.
6363 CLARK AVENUE, DUBLIN, CALIFORNIA 94568-3097
(925) 828-1440 - Fax (925) 833-8795

October 28, 1998

Mr. Omar Houry
Basic Vegetable Products
700 Airport Drive
King city, CA 93930-2501

Reference: CM 4100

Enclosed is The NFL's report on spiking portion of hydrogen peroxide residues in dried onion flakes.

Please do not hesitate to contact me if you have any questions concerning this report.

Your samples will be retained for a period of thirty days from the date of this report, at which time, unless notified to the contrary, they will be discarded.

Thank you for using the services of The National Food Laboratory.

Sincerely,

Bradford Allen, Research Chemist

cc: Mary Jo Smith, Accounting

Hydrogen Peroxide Residues in Dried Onions

NFL Project: CM 4100
Date: October 28, 1998

Summary
When onion flakes were "spiked" with hydrogen peroxide, there were no detectable residues up to the 500 ppm level. When spiked at 500 ppm, the recovery of added hydrogen peroxide was 44.6%.

Principle
This procedure measures hydrogen peroxide by employing the enzyme peroxidase to catalyze the oxidation of leuco crystal violet by hydrogen peroxide.

Reference
"*Absorptiometric Determination of Hydrogen Peroxide in Submicrogram Amounts with Leuco Crystal Violet and Peroxidase as Catalyst*"; Mottola, H.A. Simpson, B.E. and Gorin, G.; Anal. Chem., 42 ,1970, pg. 410

Reagents
Horseradish Peroxidase, Type II (HRP) (Sigma Chemical Co.)
Leuco crystal violet (LCV) (Aldrich Chemical Co.)
Sodium acetate
Glacial acetic acid
Hydrochloric acid

Apparatus
Perkin Elmer Lamba II UV/VIS Spectrophotometer

Solutions

1. LCV solution – dissolve 50 mg of leuco crystal violet in 80 mL of 0.5 % hydrochloric acid and make to 100 mL volume with 0.5 % hydrochloric acid. Protect from light.

2. HRP solution – dissolve 10 mg of horseradish peroxidase in 10 mL of water. Protect from light.

3. Acetate buffer – prepare a buffer solution form equal parts of 2 M sodium acetate and 2 M acetic acid. Adjust pH to 4.5 with glacial acetic acid.

Standards

Prepare standards by diluting 35% hydrogen peroxide with water successively to achieve standard concentration in the range of 0.25 to 2.50 ug/mL.

Procedure

Blend the dried onion flakes to a powder using a blender.
Add 10 mL of distilled water to 1.0 g of sample and let sit 10 minutes.
Filter through a 0.45 membrane filter.

For standards, pipette 1 mL of each hydrogen peroxide standard into a test tube.
For samples, pipette 1 mL of filtered sample extract into test tube.
Pipette 200 uL of LCV solution each test tube.
Pipette 200 uL of HRP into each test tube.
Add 1 mL of sodium acetate buffer.
Shake to mix and immediately determine the absorbance at 596 nm.

The spiked samples were prepared by re-hydrating 1.0 g of the dried onion samples with 10 mL of hydrogen peroxide solution such that the following levels were obtained:

5 ug hydrogen peroxide/ gram of dried flake
50 ug hydrogen peroxide/gram of dried flake
100 ug hydrogen peroxide/gram of dried flake
500 ug hydrogen peroxide/gram of dried flake

Sample	Absorbance	"Blank" Corrected Absorbance	Hydrogen Peroxide (ug/mL)	Sample Weight (g)	Final Volume (mL)	Dilution Factor	Hydrogen Peroxide (ug/g)
Standard 2.50 ug/mL	2.416						
Standard 1.00 ug/mL	0.954						
Standard 0.50 ug/mL	0.456						
Standard 0.25 ug/mL	0.248						
Blank	0.013			-	-	-	
Blank	0.015			-	-	-	
Blank	0.017			-	-	-	
Blank	0.025			-	-	-	
Ave Blank	0.016						
Spike 5 ppm	0.064	0.050	0.07	1.0	10.0	-	0.7
Spike 10 ppm	0.091	0.049	0.07	1.0	10.0	-	0.7
Spike 50 ppm	0.024	0.008	ND	1.0	10.0	-	ND
Spike 100 ppm	0.043	0.027	ND	1.0	10.0	-	ND
Spike 500 ppm	>3.0	>3.0		1.0	10.0	-	>30
Spike 500 ppm (1/10 dilution)	2.069	2.053	2.11	1.0	10.0	10	211
Spike 500 ppm (1/10 dilution)	2.199	2.183	2.24	1.0	10.0	10	224
Spike 500 ppm (1/10 dilution)	2.200	2.184	2.24	1.0	10.0	10	224
Ave.							219.7

Detection limit

The detection limit of the analysis was determined from the response of five "Blank" samp.es. The " Blank" samples were prepared by analyzing the sample solutions in the same manner as the samples, except that no LCV was added.

The limit of detection (LOD) was calculated as three standard deviations above the average "blank" signal.

$$LOD = x + 3\delta$$

The following blank signals (absorbance units) were determined:

0.013
0.015
0.017
0.011
0.025
Ave = 0.016
Std deviation = 0.005

LOD = 0.016 + 3(0.0005)

= 0.032 absorbance units

From the standard this is equivalent to 0.051 ug/mL. With a 1/10 dilution of the sample to re-hydrate the sample, this corresponds to a detection limit of 0.51 ug/g dried sample.

APPENDIX II

Analysis Reports for Nutritional Profiles of Hydrogen Peroxide-Treated and Untreated Dehydrated Onion Samples (Lancaster Laboratories)

Lancaster Laboratories
A division of Thermo Analytical Inc.

LLI Sample No. MC 3001650
Collected:

Submitted: 9/ 4/98 Reported: 10/ 6/98
Discard: 10/22/98

A Control Dried Onion Sample

Account No: 07388
Basic Vegetable Products
705 E. Whitmore Avenue
PO Box 3659
Modesto CA 95358

P.O.
Rel.

CAT NO.	ANALYSIS NAME	AS RECEIVED RESULTS	LIMIT OF QUANTITATION	UNITS
0102	Moisture (Vacuum Oven)	3.67	0.01	% by wt.
0115	Total Carbohydrate	79.4	0.1	% by wt.
0117	Est. Caloric Value	374.	2.	Cal/100g
	The Estimated Caloric Value has been calculated according to the definition found in the nutrition labeling regulations printed on January 6, 1993 in CFR Part 101.9, where: Calories/100g = 4(%protein) + 9(%fat) + 4(%carbs - IDF, if requested)			
0131	Thiamin	0.48	0.007	mg/100g
0132	Riboflavin	0.29	0.03	mg/100g
0137	Vitamin C	19.	1.	mg/100g
0452	Vitamin B6 (as pyridoxine)	1.2	0.002	mg/100g
0474	Malonaldehyde (TBA)	See Below 0.25 meq/kg	0.4 LOQ 0.1 meq/kg	See Below
1543	Protein (modified Dumas)	11.5	0.1	% by wt.
	The % protein was calculated from % nitrogen using a factor of 6.25			
4192	Fat (Acid Hydrolysis)	1.1	0.1	% by wt.
)112	Ash	4.29	0.01	% by wt.

The analysis for Malanaldehyde (TBA) was subcontracted to another laboratory.

1 COPY TO Basic Vegetable Products ATTN: Mr. Dave Mirko
1 COPY TO Environ ATTN: Mr. Ted Berner

Questions? Contact your Client Services Representative
at (717) 656-2300

19:51:45 D 0002 6 632477
389 10.00 00039100 ASR000

000045

Respectfully Submitted
Art Pezzica, BA, Manager
Food and Animal Health Science

MEMBER ACIL

Lancaster Laboratories
A division of Thermo Analytical Inc.

LLI Sample No. MC 3001651
Collected:

Submitted: 9/ 4/98 Reported: 10/ 6/98
Discard: 10/22/98

B Control Dried Onion Sample

Account No: 07388
Basic Vegetable Products
705 E. Whitmore Avenue
PO Box 3659
Modesto CA 95358

P.O.
Rel.

CAT NO.	ANALYSIS NAME	AS RECEIVED RESULTS	LIMIT OF QUANTITATION	UNITS
0102	Moisture (Vacuum Oven)	3.64	0.01	% by wt.
0115	Total Carbohydrate	78.8	0.1	% by wt.
0117	Est. Caloric Value	377.	2.	Cal/100g
	The Estimated Caloric Value has been calculated according to the definition found in the nutrition labeling regulations printed on January 6, 1993 in CFR Part 101.9, where: Calories/100g = 4(%protein) + 9(%fat) + 4(%carbs - IDF, if requested)			
0131	Thiamin	0.49	0.007	mg/100g
0132	Riboflavin	0.29	0.03	mg/100g
0137	Vitamin C	20.	1.	mg/100g
0452	Vitamin B6 (as pyridoxine)	1.3	0.002	mg/100g
0474	Malonaldehyde (TBA)	See Below 0.37 meq/kg	LOQ 0.1meq/kg	See Below
1543	Protein (modified Dumas)	11.6	0.1	% by wt.
	The % protein was calculated from % nitrogen using a factor of 6.25			
4192	Fat (Acid Hydrolysis)	1.7	0.1	% by wt.
0112	Ash	4.21	0.01	% by wt.

The analysis for Malanaldehyde (TBA) was subcontracted to another laboratory.

1 COPY TO Basic Vegetable Products ATTN: Mr. Dave Mirko
1 COPY TO Environ ATTN: Mr. Ted Berner

Questions? Contact your Client Services Representative
at (717) 656-2300

19:52:02 D 0002 6 632477
389 10.00 00039100 ASR000

000046

Respectfully Submitted
Art Pezzica, BA, Manager
Food and Animal Health Science

MEMBER ACIL

Lancaster Laboratories
A division of Thermo Analytical Inc.

LLI Sample No. MC 3001652
Collected:

Submitted: 9/ 4/98 Reported: 10/ 6/98
Discard: 10/22/98

C Control Dried Onion Sample

Account No: 07388
Basic Vegetable Products
705 E. Whitmore Avenue
PO Box 3659
Modesto CA 95358

P.O.
Rel.

CAT NO.	ANALYSIS NAME	AS RECEIVED RESULTS	LIMIT OF QUANTITATION	UNITS
0102	Moisture (Vacuum Oven)	3.75	0.01	% by wt.
0115	Total Carbohydrate	79.2	0.1	% by wt.
0117	Est. Caloric Value	373.	2.	Cal/100g
	The Estimated Caloric Value has been calculated according to the definition found in the nutrition labeling regulations printed on January 6, 1993 in CFR Part 101.9, where: Calories/100g = 4(%protein) + 9(%fat) + 4(%carbs - IDF, if requested)			
0131	Thiamin	0.50	0.007	mg/100g
0132	Riboflavin	0.20	0.03	mg/100g
0137	Vitamin C	21.	1.	mg/100g
0452	Vitamin B6 (as pyridoxine)	1.4	0.002	mg/100g
0474	Malonaldehyde (TBA)	See Below 0.24 meq/kg	LOQ 0.1 meq/kg	See Below
1543	Protein (modified Dumas)	11.8	0.1	% by wt.
	The % protein was calculated from % nitrogen using a factor of 6.25			
4192	Fat (Acid Hydrolysis)	1.0	0.1	% by wt.
J112	Ash	4.27	0.01	% by wt.

The analysis for Malanaldehyde (TBA) was subcontracted to another laboratory.

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389 10.00 00039100 ASR000

000047

Respectfully Submitted
Art Pezzica, BA, Manager
Food and Animal Health Science

MEMBER ACIL

Lancaster Laboratories
A division of Thermo Analytical Inc.

LLI Sample No. MC 3001653
Collected:

Submitted: 9/ 4/98 Reported: 10/ 6/98
Discard: 10/22/98

A Treated Dried Onion Sample

Account No: 07388
Basic Vegetable Products
705 E. Whitmore Avenue
PO Box 3659
Modesto CA 95358

P.O.
Rel.

CAT NO.	ANALYSIS NAME	AS RECEIVED RESULTS	LIMIT OF QUANTITATION	UNITS
0102	Moisture (Vacuum Oven)	3.67	0.01	% by wt.
0115	Total Carbohydrate	79.6	0.1	% by wt.
0117	Est. Caloric Value	375.	2.	Cal/100g
	The Estimated Caloric Value has been calculated according to the definition found in the nutrition labeling regulations printed on January 6, 1993 in CFR Part 101.9, where: Calories/100g = 4(%protein) + 9(%fat) + 4(%carbs - IDF, if requested)			
0131	Thiamin	[illegible]51	0.007	mg/100g
0132	Riboflavin	[illegible].28	0.03	mg/100g
0137	Vitamin C	10.	1.	mg/100g
0452	Vitamin B6 (as pyridoxine)	1.3	0.002	mg/100g
0474	Malonaldehyde (TBA)	See Below 0.55 meq/kg	LOQ 0.1 meq/kg	See Below
1543	Protein (modified Dumas)	11.7	0.1	% by wt.
	The % protein was calculated from % nitrogen using a factor of 6.25			
4192	Fat (Acid Hydrolysis)	1.1	0.1	% by wt.
0112	Ash	3.97	0.01	% by wt.

The analysis for Malanaldehyde (TBA) was subcontracted to another laboratory.

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000048

Respectfully Submitted
Art Pezzica, BA, Manager
Food and Animal Health Science

MEMBER ACIL

Lancaster Laboratories
A division of Thermo Analytical Inc.

LLI Sample No. MC 3001654
Collected:

Submitted: 9/ 4/98 Reported: 10/ 6/98
Discard: 10/22/98

B Treated Dried Onion Sample

Account No: 07388
Basic Vegetable Products
705 E. Whitmore Avenue
PO Box 3659
Modesto CA 95358

P.O.
Rel.

CAT NO.	ANALYSIS NAME	AS RECEIVED RESULTS	LIMIT OF QUANTITATION	UNITS
0102	Moisture (Vacuum Oven)	3.69	0.01	% by wt.
0115	Total Carbohydrate	79.5	0.1	% by wt.
0117	Est. Caloric Value	376.	2.	Cal/100g
	The Estimated Caloric Value has been calculated according to the definition found in the nutrition labeling regulations printed on January 6, 1993 in CFR Part 101.9, where: Calories/100g = 4(%protein) + 9(%fat) + 4(%carbs - IDF, if requested)			
0131	Thiamin	0.51	0.007	mg/100g
0132	Riboflavin	0.30	0.03	mg/100g
0137	Vitamin C	9.	1.	mg/100g
0452	Vitamin B6 (as pyridoxine)	1.3	0.002	mg/100g
0474	Malonaldehyde (TBA)	See Below 0.72 meq/kg	LOQ 0.1 meq/kg	See Below
1543	Protein (modified Dumas)	11.6	0.1	% by wt.
	The % protein was calculated from % nitrogen using a factor of 6.25			
4192	Fat (Acid Hydrolysis)	1.3	0.1	% by wt.
0112	Ash	3.97	0.01	% by wt.

The analysis for Malanaldehyde (TBA) was subcontracted to another laboratory.

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Questions? Contact your Client Services Representative
at (717) 656-2300

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000049

Respectfully Submitted
Art Pezzica, BA, Manager
Food and Animal Health Science

MEMBER ACIL

Lancaster Laboratories
A division of Thermo Analytical Inc.

LLI Sample No. MC 3001655
Collected:

Submitted: 9/ 4/98 Reported: 10/ 6/98
Discard: 10/22/98

C Treated Dried Onion Sample

Account No: 07388
Basic Vegetable Products
705 E. Whitmore Avenue
PO Box 3659
Modesto CA 95358

P.O.
Rel.

CAT NO.	ANALYSIS NAME	AS RECEIVED RESULTS	LIMIT OF QUANTITATION	UNITS
0102	Moisture (Vacuum Oven)	3.70	0.01	% by wt.
0115	Total Carbohydrate	79.5	0.1	% by wt.
0117	Est. Caloric Value	375.	2.	Cal/100g
	The Estimated Caloric Value has been calculated according to the definition found in the nutrition labeling regulations printed on January 6, 1993 in CFR Part 101.9, where: Calories/100g = 4(%protein) + 9(%fat) + 4(%carbs - IDF, if requested)			
0131	Thiamin	0.46	0.007	mg/100g
0132	Riboflavin	0.25	0.03	mg/100g
0137	Vitamin C	9.	1.	mg/100g
0452	Vitamin B6 (as pyridoxine)	1.3	0.002	mg/100g
0474	Malonaldehyde (TBA)	See Below 0.75 meq/kg	LOQ 0.1 meq/kg	See Below
1543	Protein (modified Dumas)	11.5	0.1	% by wt.
	The % protein was calculated from % nitrogen using a factor of 6.25			
4192	Fat (Acid Hydrolysis)	1.3	0.1	% by wt.
0112	Ash	4.00	0.01	% by wt.

The analysis for Malanaldehyde (TBA) was subcontracted to another laboratory.

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000050

Respectfully Submitted
Art Pezzica, BA, Manager
Food and Animal Health Science

MEMBER ACIL

APPENDIX III

Curricula Vitae of Scientific Experts

VASILIOS H. FRANKOS, Ph.D.

EDUCATION

1977 Ph.D., Pharmacology and Toxicology, University of Maryland Pharmacy School

1973 M.S., Biology, University of Maryland

1970 B.A., Biology, University of Maryland

EXPERIENCE

Dr. Frankos is a Principal at ENVIRON Corporation and has over 20 years of experience in the toxicological and pharmacological evaluation of data used to assess the risks posed by foods and food additives, drugs, medical devices, cosmetics, pesticides, and environmental and occupational exposures. He has also been involved in the development of exposure and risk assessment methodology. Since joining ENVIRON, Dr. Frankos has led, contributed to, or managed hundreds of projects in these areas.

Foods and Food Additives:
Dr. Frankos has worked on a wide variety of projects evaluating the safety of foods, direct and indirect food additives, and food contaminants. As part of these food-related safety evaluations, he has developed strategies for testing new direct and indirect additives, evaluated toxicity test data to support safety determinations, prepared Generally Recognized as Safe (GRAS) reviews, performed exposure and risk assessments, and developed regulatory strategies. Dr. Frankos has also presented safety evaluations to the FDA on behalf of clients. Some of his major projects in the area of foods and food additives include:

- Provided ongoing FDA-related scientific and technical support to the Coalition for Safe Ceramicware (CSC). Performed a safety assessment of ceramic pitchers with glazes containing lead using data collected on migration of lead into a food simulant and into real foods. This assessment was submitted to the FDA as part of the CSC's comments on the FDA's proposed rule changing the action level for lead from ceramic pitchers.

- Developed direct food additive petitions and GRAS self-affirmation documents for numerous food additives including, novel fibers sources, an anti-caking agent, enzymes, sugars, and a major new class of food additives.

- Conducted a GRAS self-affirmation review, including an evaluation of safety data, of the first bioengineered food approved by the FDA. Presented this GRAS review to the FDA on behalf of the client, a major biotechnology company.

- Developed a GRAS affirmation document for a cellulose product, manufactured by a novel bacterial fermentation process, with proposed food use as a suspending/thickening agent. Designed, placed, and monitored preclinical toxicity studies required for FDA approval.

- Estimated doses posing no significant risk for chemicals that could potentially leach from packaging into food. Assessed the potential human exposure to these chemicals from migration from packaging into food. Compared the potential ingested dose to the no significant risk dose.

- Petitioned the FDA to sanction expanded use in foods of an approved food additive. Prepared a review and update of existing toxicological literature on the material and estimated the increase in exposure likely to result from proposed new uses.

- Evaluated the carcinogenic risk associated with exposure to acrylamide residues in food and methylene chloride in decaffeinated tea.

- Addressed issues relating to FDA's regulation of polychlorinated biphenyl (PCB) residues. Examined whether tolerances for PCBs in fish could be reinterpreted for less chlorinated PCBs that have lower or no carcinogenic potency. Determined necessary research to establish differences in potency between PCBs.

- Developed an innovative exposure and safety assessment for a novel single cell protein (mycoprotein) meat substitute that has been submitted to the FDA for approval.

- Conducted a simulated FDA review of a food additive petition on a new artificial sweetener submitted to the FDA by the client's competitor. Review included critical evaluation of product chemistry, efficacy, estimates of human exposure, animal and human toxicology data, pharmacokinetics and metabolism information, and the basis for determining the acceptable daily intake of the sweetener.

- Performed a detailed evaluation of toxicity and carcinogenicity studies sponsored by a major drug company and studies from the published literature for the company's non-nutritive sweetener and assessed the toxicological significance to humans. Assisted in submission of a food additive petition. Provided continued regulatory support during the FDA review process.

Human and Veterinary Drugs, Medical Devices, and Cosmetics:
Dr. Frankos has provided scientific and regulatory guidance to clients in the human and veterinary drug, medical device, and cosmetic industries. He has been involved in identifying and assessing the risks to humans associated with exposure to constituents of these products. He has assisted clients in these industries in interacting with the FDA and has assisted them in complying with all aspects of FDA regulations. Some of his major projects in the areas of drugs, medical devices, and cosmetics include:

- Reviewed two large epidemiological studies on the differences in adverse drug reaction rates between two types of radiographic contrast media. Prepared a safety review document on animal and human literature on contrast media.

- Performed an independent evaluation of a New Drug Application (NDA) submission to the FDA, with emphasis on review of efficacy studies.

- Assisted the medical device manufacturer in complying with FDA's post-approval requirements for its device including compliance with the Medical Device Reporting (MDR) rule, submission of updates to the PMA application, and ensuring that all labeling and marketing materials are in compliance with FDA regulations. Designed a post-marketing clinical trial for the device to comply with FDA recommendations.

- Evaluated the potential carcinogenic risks to humans of an over-the-counter (OTC) medication that is applied to the skin. Prepared a report on these findings that was submitted to the FDA.

- Prepared and submitted to the FDA a New Drug Application (NDA) for a drug that holds promise for dramatically decreasing the high percentage of reocclusion that occurs in angioplasty patients.

- Assisted a major pharmaceutical manufacturer in assessing potential health risks associated with a specific ingredient of various over-the-counter (OTC) drugs.

- Critically evaluated both published and unpublished studies on a psychoactive drug and rendered an opinion to the client on potential health effects of the drug and whether a no-observed-effect level (NOEL) had been established.

- Provided guidelines for subchronic testing to evaluate the safety for human use of an allergen desensitizer that was produced by polymerizing the allergen through a glutaraldehyde treatment.

- Analyzed the potential risk to humans resulting from the use of Furazolidone as an animal drug. Determined an estimate of this risk and presented the estimate to the FDA at a public hearing.

- Assisted a major manufacturer of veterinary drug products in developing an approach to dealing with mouse liver tumors and their usefulness as evidence of carcinogenicity.

- Reviewed and evaluated a New Animal Drug Application for FDA submission. Advised on the necessity of future studies.

- Assembled an expert panel to address the safety of an antimicrobial agent, extracted from a plant source, for use in oral hygiene products (e.g. toothpaste and oral rinse). The evaluation included a review of the preclinical and clinical toxicologic database, analysis of exposure, and determination of margin of safety associated with the proposed oral uses.

- Critically evaluated the evidence cited by FDA as the basis for considering nitrofuran animal drugs to be carcinogenic under the meaning of the Delaney Clause of the Federal Food, Drug, and Cosmetic Act.

- Reviewed toxicity data to be submitted in support of an Investigational Device Exemption (IDE) for an implantable medical device. Recommended and monitored the performance of supplemental tests, performed an exposure assessment of substances leaching from the device into the systemic circulation, characterized the risk to health from such exposures, and assisted in the presentation of these findings to the FDA.

- Evaluated toxicity data on the materials used in a device intended to be implanted in the abdominal cavity. Examined the adequacy of the existing data on the device material, the safety of the material used, and the safety of the proposed replacement material. Recommended studies to improve the data for submission to the FDA.

- Conducted a quantitative risk assessment on numerous color additives used in dermally applied cosmetics including an evaluation of toxicity, an analysis of exposure, and a determination of quantitative risks.

- Performed a hypothetical risk assessment for two colors used in cosmetics, based on the assumption that, if tested, they would produce tumors in rats. Demonstrated that such an outcome would still allow continued safe use of these colors in cosmetics.

Pesticides:
Dr. Frankos has assisted U.S. and foreign manufacturers in obtaining EPA and California registration of agricultural, forestry, and homeowner use pesticide products. Some of his major projects in the area of pesticides include:

- Reviewed EPA's assessment of dietary oncogenic risk of two fungicides and advised the manufacturers of additional data needed to perform a quantitative risk assessment.

- Designed and supervised a field study to estimate exposure to a pesticide during "worst case" application. The study monitored the application of the chemical, measured exposure of the user during various phases of application and determined the effect of protective clothing on exposure.

- Reviewed the results of an aquatic organism field monitoring study and its supporting laboratory data for a major manufacturer of agricultural chemicals.

- Evaluated toxicity and prepared a risk assessment for residues of a fungicide in imported wines. Counseled client on process necessary to receive an EPA import tolerance for the fungicide. Advised client on additional data needed to support a tolerance.

- Designed and monitored toxicology studies for a German firm required for registration of a plant growth promotor and assisted in submitting data to the EPA.

- For a West German pesticide manufacturing company wishing to purchase the patent rights to a new pesticide developed in the U.S., provided counsel on the acceptability of the available data to EPA and OECD and the further data needed to obtain a registration in the U.S.

Environmental and Occupational Exposures:
Dr. Frankos has directed numerous exposure and risk assessments involving hundreds of chemicals that have been associated with industrial processes, toxic waste or municipal incinerators, and hazardous waste sites. These assessments have used computerized models and include all routes of exposure. Some of his major projects in the areas of environmental and occupational exposures include:

- Performed a safety assessment for the consumption of drinking water in contact with a piece of equipment that could potentially release lead, including an estimation of 1990 baseline blood lead levels for four subpopulations using the Integrated Uptake/Biokinetic Model and a determination of the maximum acceptable concentration of lead in drinking water that was potentially in contact with the equipment. Collected and reviewed information on factors that affect the leachability of lead into drinking water.

- Assisted manufacturers of the plasticizer di-(2-ethylhexyl) phthalate (DEHP) in developing a method for estimating exposure resulting from the chemical's presence in polyvinyl chloride (PVC) consumer products such as vinyl-covered furniture, vinyl wallpaper, flooring, and shower curtains.

- Critically reviewed acrylamide's carcinogenic activity in Fischer 344 rats and designed a new cancer bioassay in rats that will improve risk assessments for acrylamide.

- Reviewed the scientific basis for establishing safety factors needed to protect workers from reproductive toxicity associated with glycol ether exposure.

- Reevaluated the data from a National Cancer Institute (NCI) bioassay on dibutyltin diacetate to resolve discrepant interpretations by NCI and FDA.

- Reviewed FDA and National Toxicology Program (NTP) evaluations of the bioassay on dimethylterephthalate and rendered an opinion on the adequacy of the NTP and FDA decisions.

- Supported the EPA Office of Solid Waste in developing measures of inherent toxicity which can be combined with exposure estimates to provide a relative ranking for scheduling hazardous solid waste.

- Provided scientific litigation support for a municipality in which its waste treatment plant and landfill were contaminated with PCBs.

- Participated in a number of projects examining the developmental, embryotoxic, and teratogenic effects of lead observed in animals, including the effects of lead on the reproductive systems of male and female rats. Recommended a no-observed-adverse-effect level (NOAEL) for lead.

Exposure and Risk Assessment Methodology Development:
Dr. Frankos has participated in the development of new exposure and risk assessment methodologies for federal and state regulatory agencies. He has also been integral in the development of exposure and risk modeling software. Some of his major projects in these areas include:

- Developed a background document for the EPA on reproductive toxicity risk assessment for use in drafting interagency risk assessment guidelines.

- Directed development of a scheme for the EPA that allows severity of toxic effects to be incorporated into safety evaluations of EPA regulated products.

- Summarized and compiled comments received by EPA on their proposed guidelines (1985) for developmental toxicity assessment.

- Assisted in evaluating EPA's procedures for estimating safe short-term exposure limits and in developing an alternative method that could be uniformly used by the entire agency.

- Assisted in the development of criteria for listing chemicals as developmental toxicants under California's Proposition 65.

- Directed the development of a computer software system, ERMA (Exposure and Risk Modeling Assistant) that enables ENVIRON to provide high quality, scientifically defensible evaluations of potential exposures and resultant risk.

Before joining ENVIRON Corporation, Dr. Frankos held the following positions:

- Associate Director, Life Sciences Division, Clement Associates. In that position he had the following experience:

    - Supervised a staff of eight scientists who assessed the risk posed by environmental contaminants, occupational carcinogens, pesticides, drugs, commercial product constituents, and food additives. Many of these projects involved evaluating human and animal toxicology data for use in conducting human risk assessments. This position

required management of time constraints, budgetary limitations, and personnel allocations in a manner that provided the client with a scientifically defensible document.

- Directed preparation of reports for industry clients that included "Safety Assessment Strategies for Feminine Hygiene Products"; "The Impact of a Proposed Salicylate Warning on the Risk Associated with Diseases and Conditions in Children"; and "A Proposed Mechanism of Action for a Carcinogenic Hair Dye Ingredient."
- Directed and prepared a report to OSHA entitled "Formaldehyde Risk Assessment for Occupationally Exposed Workers" and assisted in developing guidelines for interspecies data extrapolation for use by OSHA in its revised cancer policy.
- Provided litigation toxicity support to private and industry clients and assisted private concerns in the development of testing protocols for the purposes of fulfilling regulatory requirements.
- Served as expert reproductive toxicity witness in the House of Representative's hearing on the "Relationships of Exposure to Toxic Chemicals and Reproductive Impairment."

• Staff Science Advisor, Office of Health Affairs, Commissioners Office, Food and Drug Administration.

- Provided professional scientific expertise in pharmacology, toxicology, biochemistry, and biology requisite to the effective accomplishment of the Agency's scientific overview and leadership function. Served as technical expert, scientific advisor, and liaison of the Commissioner at the Bureau level on matters relevant to toxicologic and pharmacologic safety assessment of toxic substances to which humans and animals are exposed.
- Responsibilities included performing risk assessments on compounds (such as PCB's, methapyraline, caffeine, etc.) that could be utilized by the Commissioner's office in choosing between various regulatory options. Routinely reviewed toxicity data on compounds as diverse as caffeine, methylsalicylate, xylitol, and sodium nitrite. Provided litigation support and testified as expert toxicology witness at the Administrative Law Judge hearing on the safety of cyclamate.
- Participated in the National Toxicology Program (NTP). Duties included review of agency nominations for toxicity testing by NTP, research planning for the regulatory needs of FDA, preparation of the Annual Carcinogen Report, and participation in numerous NTP workgroups.
- Interagency and international initiatives included chairing the Interagency Regulatory Liaison Group (IRLG) Workgroup on Reproductive Toxicity Risk Assessment. Planned, coordinated, and published a three-day symposium entitled, "The Effects of Foods and Drugs on the Development and Function of the Nervous System." Chaired and organized a national workshop on Reproductive Toxicity Risk Assessment.
- Served as Project Director of a contract with the Environment Teratology Information Computer Division, Oak Ridge National Research Laboratory to develop computerized teratology literature data extraction, indexing, and collation. This data base system is being integrated into the ETIC master computer file and will be manipulated through the INQUIRE data base management system.

- Senior Toxicologist, Division of Toxicology, Center for Food Safety and Applied Nutrition, Food and Drug Administration.

  - Responsible for the toxicologic evaluation of compounds of special interest to the agency. Required expert review of data on carcinogenicity, promotion, reproduction, teratology, and pharmacokinetics. Presented scientific evaluations to congressional, departmental, and agency directors. Represented the agency on sensitive scientific issues. Areas of emphasis included evaluation of toxicity data on artificial sweeteners (saccharin, cyclamate, xylitol, etc.), development of reproductive toxicity risk assessment criteria, pharmacokinetics evaluation of compounds (methylene chloride, sodium nitrite, saccharin, etc.), and risk assessment.
  - Directed the development of a PC computer network to be used by the Review Toxicologist of the FDA Bureau of Foods. This system allows direct access to toxicology data bases at NLM, Oak Ridge, Dialog, and extensive FDA internal data bases and full manipulation, storage, and collation of personalized literature data bases.

- Toxicologist, Division of Toxicology, Bureau of Foods, Food and Drug Administration.

  - Responsible for toxicologic review of substances used as direct and indirect food additives. Duties required discussions with manufacturers, formulators, toxicologists, universities, and other agencies on experimental procedures for showing safety and estimating risk.
  - Additional duties and accomplishments included primary involvement in planning, testing, and implementing new proposed regulations that direct the priority assessment review of all food additives. Duties included designing and implementing modern toxicity testing protocols, protocol quality parameters, criteria for utilizing toxicity data, and computer compatible toxicology test summarization forms. Co-led a 12 person toxicology cyclic review team. This endeavor was awarded a commendable service citation.
  - Served as the toxicology member on the Program Advisory Board for the FDA's effort to modernize the storage and retrieval of safety information in the Bureau of Foods. Over two million dollars was expended for the computerization and microfiching of all Bureau petition files. This system is now fully operational within the FDA and is called SIREN.

- Research Assistant, Department of Pharmacology and Drug Abuse, Maryland Psychiatric Research Center.

  - Laboratory responsibilities included the daily analysis of the catecholamines and their metabolites in the urine of patients under different drug therapies. Used column chromatography to separate the monoamines and their metabolites with subsequent fluorometric determinations of their amounts. Techniques involved using radioisotopic methods to determine monoamine oxidase kinetics, substrate km, and oxygen

requirements and preparing mitochondrial isolates to study by oxygraphic assay and radioisotopic methods.

- Clinical responsibilities included the collection, collation, and statistical analysis of data obtained by researchers in various disciplines, such as clinical and physiological psychology, biochemistry, and pharmacology. Assisted in the design, implementation, and statistical analysis of a study concerning the use of naloxone and cyclazocine as narcotic antagonists in a population of paroled drug addicts. Implementation of the study involved administering, scoring, and statistically analyzing psychodiagnostic and intelligence tests.

HONORS

1980	FDA Commendable Service Award for Direct Food Additive Cyclic Review
1969-70	Baltimore University Club Scholarship
1966-67	American Hellenic Education Scholarship

PROFESSIONAL ACTIVITIES AND MEMBERSHIPS

Invited presentation entitled "Developmental and Reproductive Toxicity Testing of Implantable Medical Devices." Presentation for: 1996 Summer Short Course Series on Medical Device Biocompatibility: From Material Screening to Final Product Testing. Sponsored by: Case Western Reserve University. July 18-19, 1996, Baltimore, Maryland.

Invited presentation entitled "Risk Assessment: What is it? How can I use it?" Regional Meeting of the Association of Official Analytical Chemists (AOAC), October 27, 1994, College Park, Maryland.

Invited presentation entitled "Testing Requirements for Medical Devices" Annual Genetic Toxicology Workshop, May 3-5, 1993, Rockville, Maryland.

Society of Regulatory Toxicology and Pharmacology 1990 -

Food and Drug Law Institute 1990 -

Guest Lecturer, University of Vermont Law School "Risk Assessment at the Law" June 4-14, 1990, Burlington, Vermont.

Invited presentation entitled "Review of Safety and Toxicity of Sanguinaria and Sanguinarine" Symposium on Sanguinaria, April 25, 1990, Toronto, Ontario, Canada.

Invited presentation entitled "Health Risks and Safety Precautions" PCB Compliance, Cleanup and Disposal, March 27-28, 1990, Toronto, Ontario, Canada.

Environmental Law Institute 1989 -

Invited panel member "Weight of Evidence Considerations in Identifying Reproductive and Developmental Toxicants" Risk Assessment Issues in Developmental and Reproductive Toxicology, Sept. 18-19, 1989, Berkeley, California.

Invited presentation entitled "Health Risk and Safety Precautions" Current Issues in PCB Compliance, May 24-25, 1989, Toronto, Canada.

Regulatory Affairs Professionals Society 1988 -

Invited presentation entitled "Risk Assessment for Effects Other than Cancer" 1986 Conference for Food Protection, Aug. 17-20, 1986, Ann Arbor, Michigan.

Invited work group member at the EPA sponsored "Consensus Workshop on the Evaluation of Maternal and Developmental Toxicity" May 12-14, 1986, Rockville, Maryland.

Co-author of an invited paper entitled "Acrylonitrile as a Carcinogen: Research Needs for Better Risk Assessment" presented at the International Conference on "Occupational and Environmental Significance of Industrial Carcinogens" October 7-9, 1985, Milan, Italy.

Invited presentation entitled "FDA Perspectives on the use of Teratology Data for Human Risk Assessment" Symposium on "Risk Assessment for Developmental Toxicity" Annual meeting of the Society of Toxicology, March 13, 1984, Atlanta, Georgia.

Guest Lecturer and Expert Consultant to the Environmental Teratology Information Computer Division, Oak Ridge National Research Laboratory. 1982.

Expert Witness before the U.S. House of Representatives Committee on Science and Technology hearing on the "Relationship of Exposure to Toxic Chemicals and Reproductive Impairment," 1982.

Guest speaker, FDA National Scientific Health Professionals Meeting; spoke on the National Toxicology Program. 1981.

Member, National Toxicology Program Chemical Evaluation Committee. 1979-1982.

Member, National Toxicology Program Annual Carcinogen Report Workgroup. 1979-1982.

Invited workshop panel member, Workshop on Biological and Statistical Implications of the ED Study on Related Data Bases, Mt. Sterling, Ohio; sponsored by the Society of Toxicology for the National Center for Toxicological Research. 1981.

Chairman - Interagency Regulatory Liaison Group - Reproductive Toxicity Risk Assessment Group. 1980-1981.

Chairman and Organizer of the IRLG - Reproductive Toxicity Risk Assessment Workshop held at FDA, Rockville, MD. 1981.

Participated in preparation of the National Science Foundation Third Annual Science and Technology Report. 1980.

Participated in Preparation of the National Science Foundation Five-Year Science Outlook. 1980.

Participated in publication of the First Annual Report on Carcinogens (DHHS/NTP). 1980.

Organizer and lecturer for a State Department and DHHS/FDA sponsored course conducted for the National Organization for Drug Control and Research (Cairo, Egypt), entitled: "A Course in Chronic and Reproductive Toxicity Testing and Risk Assessment." 1980.

Guest lecturer at FDA Consumer Exchange Meeting: Use of Risk Assessment for Decision-Making. 1980.

Co-chairman and organizer of the Fifth FDA Science Symposium on Effects of Foods and Drugs on the Development and Function of the Nervous System: Methods for Predicting Toxicity. Delivered presentation entitled "Symposium Summary and Future Directions for Neurotoxicology Testing." 1979.

Expert witness FDA Administrative Law Judge hearing on the Safety of Cyclamate Used as an Artificial Sweetener. 1979.

PUBLICATIONS

Hester, T.R., N.F. Ford, P.J. Gale, J.L. Hammett, R. Raymond, D. Turnbull, V.H. Frankos, and M.B. Cohen. 1997. Measurement of 2,4-toluenediamine in urine and serum samples from women with même or replicon breast implants. *Plastic and Reconstructive Surgery*. 100(5):1296-1298.

Silverstein, B., K.M. Witkin, V.H. Frankos, and A.I. Terr. 1997. Assessing the Role of the Biomaterial Aquavene in Patient Reactions to Landmark Midline Catheters. *Regulatory Toxicology and Pharmacology*. 25(1).

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Rodricks, J.V., V.H. Frankos, and L.M. Plunkett. 1995. Food Additives. In: Regulatory Toxicology. C.P. Chengeliss, J.F. Holson and S.C. Gad (eds.) Raven Press, New York, New York, 51-82.

Spiegel, J.E., R. Rose, P. Karabell, V.H. Frankos, and D.F. Schmitt. 1994. Safety and Benefits of Fructooligosaccharides as Food Ingredients. *Food Technology*. 85-89.

Redenbaugh, K., T. Berner, D. Emlay, V. Frankos, W. Hiatt, C. Houck, M. Kramer, L. Malyj, B. Martineau, N. Rachman, L. Rudenko, R. Sanders, R. Sheehy, and R. Wixtrom. 1993. Regulatory Issues for Commercialization of Tomatoes with an Antisense Polygalacturonase Gene. *In Vitro Cell. Dev. Biol.* 29:17-26.

Frankos, V.H., D.F. Schmitt, L.C. Haws, A.J. McEvily, R. Iyengar, S.A. Miller, I.C. Munro, F.M. Clydesdale, A.L. Forbes, and R.M. Sauer. 1991. Generally Recognized as Safe (GRAS) Evaluation of 4-Hexylresorcinol for Use as a Processing Aid for Prevention of Melanosis in Shrimp. *Regulatory Toxicology and Pharmacology* 14:202-212.

Wilcock, K.E., A.B. Santamaria, V.H. Frankos, H.W. Fischer, F. Laden, E.A. Platz, and B.A. Jackson. 1990. Perspectives on Adverse Reaction Rates Associated with the Use of High Osmolar Ionic and Low Osmolar Nonionic Contrast Media. *Journal of the American College of Toxicology* 9(6):563-607.

Frankos, V.H., D.J. Brusick, E.M. Johnson, H.I. Maibach, I. Munro, R.A. Squire, and C.S. Weil. 1990. Safety of Sanguinaria Extract as Used in Commercial Toothpaste and Oral Rinse Products. *Journal of the Canadian Dental Association* 56(7 Suppl):41-47.

Schmitt, D., V. Frankos, and D. Richardson. 1990. Toxicologic Evaluation of Sanguinaria Extract. Eleventh Annual Meeting of the American College of Toxicology. Program and Abstracts. Abstract.

Schmitt, D., V. Frankos, J. Westland, and T. Zoetis. 1990. Toxicological Evaluation of Cellulon™ Fiber: Genotoxicity, Acute and Subchronic Toxicity. Eleventh Annual Meeting of the American College of Toxicology. Program and Abstracts. Abstract.

Rudenko, L., J. Adgate, M. Aponte-Pons, T. Berner, V. Frankos, R. Gregory, C.K. Lintner, N. Rachman, W. Sherman, T. Winters, and R. Wixtrom. 1990. Application of Risk Assessment Methodology to Genetically Engineered Food Products: A Generic Approach. Society for Risk Assessment. Abstract.

Frankos, V., M. Stedman, and M.A. Friedman. 1989. A lifetime oncogenicity study of acrylamide administered to F344 rats in the drinking water. Tenth Annual meeting of the American College of Toxicology. Program and Abstracts. p.26. Abstract.

Hanson, C.F., V.H. Frankos, and W.O. Thompson. 1989. Bioavailability of oxalic acid from spinach, sugar beet fibre and a solution of sodium oxalate consumed by female volunteers. Fd. Chem. Toxic. 27,3:181-184.

Frankos, V., L.H. Dulak, M.A. Fiedman. 1989. Use of risk assessment in the statistical design of a carcinogenicity bioassay of acrylamide. The Toxicologist 9:179. Abstract.

Strother, D.E., R.W. Mast, R.C. Kraska, and V. Frankos. 1988. Acrylonitrile as a carcinogen. Research needs for a better risk assessment. Annals of the New York Academy of Sciences 534:169-178.

Hanson, C.F., V.H. Frankos, and W.O. Thompson. 1988. Low dietary availability of oxalic acid present in refined sugar beet pulp compared to spinach and sodium oxalate. The Toxicologist 8:88. Abstract.

Strother, D.E., R.W. Mast, R.C. Krashka, and V. Frankos. 1988. Acrylonitrile as a Carcinogen: Research Needs for Better Risk Assessment, Annals of the New York Academy of Sciences 534:169-178.

Schwetz, A. Bernard, R.W. Tyl et al. 1987. Consensus workshop on the evaluation of maternal and developmental toxicity work group III report: Low dose extrapolation and other considerations for risk assessment - models and applications. Teratogenesis, Carcinogenesis, and Mutagenesis 7:321-327.

Frankos, V.H. and S.H. Rieth. 1987. Safety factors applied to various FDA pregnancy class drugs. The Toxicologist 7. Abstract.

Kimmel, C.A., G.L. Kimmel, and V. Frankos. 1986. Editors IRLG Workshop on Reproductive Toxicity Risk Assessment. *Environmental Health Perspectives,* Vol 66, 193-221.

Rodricks, V. Joseph, V. Frankos, D. Turnbull, R.G. Tardiff. 1986. Risk assessment for effects other than cancer. In Food Protection Technology. Proceedings of the 1986 Conference for Food Protection. Lewis Publishers, Inc.

Frankos, V.H. 1985. FDA perspectives on the use of teratology data for human risk assessment. *Fundamental and Applied Toxicology.* Vol. 5, 615-625.

Flamm, W.G. and V. Frankos. 1985. Formaldehyde: Laboratory Evidence. In "Interpretation of Negative Epidemiological Evidence for Carcinogenicity." IARC Scientific Publication 65.

Siegel, D.M., V.H. Frankos, and M.A. Schneiderman. 1983. Formaldehyde risk assessment for occupationally exposed workers. *Regulatory Tox. and Pharm.* 3, 355-371.

Frankos, V.H. 1982. Relationship of exposure to toxic chemicals and reproductive impairment. Expert testimony for Committee on Science and Technology, U.S. House of Representatives July 27, 1982. United State Government Printing Office.

Frankos, V.H. 1982. Qualitative comparison of chemical teratogenesis in humans and animal species (Abstract). Third Annual Meeting of the American College of Toxicology, Washington, D.C.

Siegel, D.M., V.H. Frankos, and M.A. Schneiderman. 1982. Formaldehyde risk assessment for occupationally exposed workers (Abstract). Third Annual Meeting of the American College of Toxicology, Washington, D.C.

Frankos, V.H. and J. Wassom. 1982. Computerized teratology literature data extraction, indexing, and collation (Abstract). *Teratology.* 25:2 80A.

Frankos, V.H. Symposium Summary and Suggested Future Directions for Detection of Neurotoxicity. 1980. In The Effects of Foods and Drugs on the Development and Function of the Nervous System: Methods for Predicting Toxicity. Edited by Gryder, R.M. and Frankos, V.H. U.S. Department of Health and Human Services, Food and Drug Administration, Publication No. DHHS/FDA 80-1076.

Frankos, V.H. 1980. Reproductive toxicity risk assessment task group: Outline of work plan and request for comments. Federal Register 45:63553-63554.

Gryder, R.M. and V.H. Frankos (eds.). 1980. The Effects of Foods and Drugs on the Development and Function of the Nervous System: Methods for Predicting Toxicity. U.S. Department of Health and Human Services, Food and Drug Administration.

Frankos, V.H. and R. Platt. 1976. Glycerol accumulation and water content in larvae of *Limenitis archippus*: Their importance to winter and survival. *J. Insect Physiol.* 22:623-623.

Frankos, V.H. and G. Butterbaugh. 1976. Characterization of norepinephrine metabolism following simultaneous intraventricular injection of H^3-L-tyrosine and C^{14}-DL-norepinephrine. *Pharmacologist* 18:135.

Messiha, K.F., E. Bakutis, and V.H. Frankos. 1973. Simultaneous separation of acid metabolites of catecholamines: Application to urine and tissue. *Clin. Chim. Acta.* 45:159-164.

- Critically evaluated the procedures used by EPA for estimating the health risks associated with diesel and gasoline engine emissions.
- Prepared comments for submission to EPA on its proposed changes in the regulation of PCBs.
- Prepared comments for submission to EPA on its proposed regulations governing the use of acrylamide grouts used in sewer lines.
- Reviewed toxicity evaluations and risk assessments of pesticides used in forestry for two trade associations.
- Managed litigation support cases involving alleged health impairment due to exposure to pesticides and consumer products.
- Provided technical guidance and review for evaluations of the toxicity and carcinogenic potential of a variety of pesticides for several pesticide manufacturers.
- Performed independent risk assessments of a large number of chemicals for several consumer product manufacturers subject to the provisions of California's "Proposition 65."
- Supervised the preparation of reports evaluating the safety of several implanted medical devices.
- Supervised the preparation and submission of many Premanufacture Notices (PMNs) and Low Volume Exemptions (LVEs) to EPA under the Toxic Substances Control Act (TSCA).
- Provided technical guidance and review of reports evaluating the potential health hazards associated with several "Superfund" and other hazardous waste sites.
- Contributed to the evaluation of the safety of an over-the-counter drug product.
- Supervised the preparation of a detailed review of the toxicology of chromium and nickel and their compounds.
- Provided review and technical guidance in work aimed at improving methods used by EPA for assessing risks from mixtures of chemicals.
- Contributed to a review of the potential risk associated with exposure to heat-treated amorphous silica.
- Developed training materials for a workshop on risk assessment for EPA's Office of Solid Waste.

- Supervised and contributed to the development of a comprehensive procedure for assessing hazards from acute and short-term exposure to chemicals.
- Supervised the preparation of a detailed analysis of the health hazards of ethyl carbamate (urethane).
- Supervised the preparation of a risk assessment of 1,3-butadiene.
- Contributed to the preparation of a review of data on the mechanism of action of 2,3,7,8-tetrachlorodibenzo-p-dioxin as a carcinogen.
- Supervised and contributed to the preparation of a detailed review of the potential impact on human health of diesel particulate emissions.
- Prepared a document reviewing available data on procedures for interspecies extrapolation.
- Assisted companies with the preparation of data packages for submission to regulatory agencies (EPA and FDA) in support of registration of various pesticides, food and feed additives, and medical devices.
- Contributed to the development of a ranking scheme for identifying industrial chemical sites where an acute toxicity hazard might exist.
- Prepared a risk assessment and proposed action levels and treatment methods for a city drinking water supply board whose supply, coming from ground water, is contaminated with the pesticides ethylene dibromide and dibromochloropropane.
- Contributed to the development and testing of a scheme to score the severity of toxic effects produced by chemicals for EPA's Environmental Criteria and Assessment Office.
- Prepared a review of the relationship between the induction of peroxisome proliferation in the liver and adverse health effects.
- Prepared an analysis of existing understanding of the risks of benzene and associated uncertainties, and proposed a research program that would most efficiently increase our understanding and reduce the uncertainties.
- Contributed to a major review of the available data on the toxicity of gasoline vapor, the uncertainties in that information, and its potential utility for risk assessment.
- Prepared a report recommending a safe level of soil contaminants at a site subject to the New Jersey Environmental Cleanup Responsibility Act (ECRA).

- Prepared a report describing how the conduct of risk assessment by the federal government could be improved using formaldehyde as an example.

- Prepared a review and sensitivity analysis of a risk assessment of benzene prepared by California Department of Health Services.

- Devised and documented a risk assessment procedure for polychlorodibenzo-p-dioxins (PCDDs) and polychlorodibenzofurans (PCDFs) for a client with a problem with PCDD and PCDF contamination.

- Made a major contribution to a comprehensive assessment of the toxicity and potential health risks of an important food additive.

- Reviewed safety data on a medical device and advised the client how likely concerns of FDA could be met.

- Reviewed EPA's risk assessment of ethylene dibromide (EDB) and contributed to a report offering an alternative, more scientifically rigorous, assessment of potential risks from EDB in grain products.

- Presented a paper on the public health risks of EDB at the annual meeting of the American Chemical Society.

- Reviewed an assessment by EPA of potential reproductive risks of glycol ethers and pointed out the lack of scientific support for some of the procedures used by EPA and offered alternatives.

- Reviewed the toxic hazards of trihalomethanes that may be formed during chlorination of drinking water and the hazards associated with alternative water treatment methods.

- Prepared an assessment of the potential health risks to workers and neighboring residents from the operation of a system for cleaning up contaminated ground water.

- Prepared an analysis of the likelihood of serious health risk from impurities in color additives used in cosmetics.

- Prepared a full scale risk assessment (including review of data on the carcinogenicity, genotoxicity, and possible mechanisms of action) of di(2-ethylhexyl)phthalate.

- Prepared a review of the results of short-term testing for carcinogenicity of extracts of a suture material for submission to FDA.

- Reviewed data concerning the safety of an ingredient of several over-the-counter drugs.

- Prepared a review of the nature of the congenital abnormality Down's Syndrome and its causes.

- Reviewed data on the efficacy of ultrasonic devices for repelling rodents and insects.

- Prepared a carcinogenicity risk assessment for a metabolite of a proposed pesticide.

- Contributed to the development and application of models to score the relative risks of toxic waste streams to humans and the environment and of hazardous waste sites to humans for EPA's Office of Solid Waste.

- Prepared a review of the nature and carcinogenicity of polychlorinated biphenyls (PCBs).

- Prepared a review of the toxicology of a chemical proposed as a human drug in support of an application by a drug company to FDA.

- Participated in a review of occupational safety and health in the flavor and fragrance industries.

- Reviewed data on the potential carcinogenicity of a component of a polymer proposed for use as a beverage container.

- Participated in analyses of the health hazards to individuals exposed to toxic chemicals from dump sites.

- Prepared analyses of the possible hazards to consumers from several color additives used in cosmetics.

Before joining ENVIRON, Dr. Turnbull held the following positions:

- Senior Staff Scientist at Clement Associates. While at Clement, Dr. Turnbull was involved in a large number of projects relating to health and safety including the following:

  - For OSHA, played a major role in the review of the 1980 Cancer Policy and consideration of possible amendments including the use of quantitative risk assessment and the utility of short term tests for carcinogens in regulation of carcinogens.

  - Prepared reviews of toxicology of hazardous chemicals used by applicants for Environmental Impairment Liability insurance.

  - Prepared detailed reviews of the toxicology of polychlorinated biphenyls (PCBs) for clients with a PCB-contamination problem.

- Acted as Project Leader for a major contract with EPA for the consolidation, review, and analysis of data in support of pesticide registration.

- Contributed to a review of the safety of foods and food ingredients.

- Visiting Research Fellow at National Cancer Institute, Bethesda, Maryland. Performed mutagenesis, cytogenetics and cell transformation studies using Chinese hamster and human cells to aid understanding of the relationship between mutagenesis and carcinogenesis.

- Research Student, Medical Research Council Cell Mutation Unit, University of Sussex, England. Studied chemical mutagenesis by alkylating agents in Chinese hamster cells.

- Research Assistant, Institute of Virology, University of Glasgow, Scotland. Studied the effects of nucleosides and nucleotides on the growth of Syrian hamster cells in suspension.

AWARDS

Visiting Research Fellowship, National Cancer Institute, Bethesda, MD 1975-1978

Medical Research Council Research Studentship 1972-1975

PROFESSIONAL MEMBERSHIPS

Society of Toxicology
Society for Risk Analysis
Environmental Mutagen Society
New York Academy of Sciences

PUBLICATIONS

Hester, T.R., N.F. Ford, P.J. Gale, J.L. Hammett, R. Raymond, D. Turnbull, V.H. Frankos, and M.B. Cohen. 1997. Measurement of 2,4-toluenediamine in urine and serum samples from women with même or replicon breast implants. *Plastic and Reconstructive Surgery*. 100(5):1296-1298.

J.V. Rodricks, L. Rudenko, T.B. Starr, and D. Turnbull. 1997. Risk Assessment, in Comprehensive Toxicology, edited by I.G. Sipes, C.A. McQueen, A.J. Gandolfi, Elsevier Science Ltd., Oxford, UK, pp.315-388.

Turnbull, D., R.J. Machado, , and R.E. Boberg. 1994. Safety assessment of HCFC-141b: Use as a blowing agent for insulation in building construction and refrigeration. *Reg. Toxicol. Pharmacol.* 19:282-296.

Couture Haws, L., B.A. Jackson, D. Turnbull, and W.E. Dressler. 1994. Two approaches for assessing human safety of Disperse Blue 1. *Reg. Toxicol. Pharmacol.* 19:80-96.

Plunkett, L.M., D. Turnbull, and J.V. Rodricks, 1992. Differences between adults and children affecting exposure assessment. In P.S. Guzelian, C.J. Henry, and S.S. Olin, eds. *Similarities and Differences Between Children and Adults: Implications for Risk Assessment.* ILSI Press, Washington, DC. pp. 79-94.

Turnbull, D., J.V. Rodricks, and S.M. Brett. 1990. Assessment of the potential risk to workers from exposure to 1,3-butadiene. *Environ. Health Perspect.* 86:159-171.

Gough, M. and D. Turnbull. 1990. Estimating the cancer risks of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. In C.C. Travis and H.A. Hattemer-Frey, eds. *Municipal Waste Incineration and Human Health.* CRC Press, Boca Raton, FL.

Turnbull, D. and J.V. Rodricks. 1989. A comprehensive risk assessment of DEHP as a component of baby pacifiers, teethers and toys. In Paustenbach, D.J. ed. *The Risk Assessment of Environmental Hazards: A Textbook of Case Studies.* John Wiley & Sons, New York. pp. 868-896.

Brett, S.M., J.S. Schlesinger, D. Turnbull, and R.J. Machado. 1989. Assessment of the public health risks associated with the proposed excavation of a hazardous waste site. In Paustenbach, D.J. ed. *The Risk Assessment of Environmental Hazards: A Textbook of Case Studies.* John Wiley & Sons, New York. pp. 427-458.

Brown, S.L., S.M. Brett, M. Gough, J.V. Rodricks, R.G. Tardiff, and D. Turnbull. 1988. Review of interspecies risk comparisons. *Regulatory Toxicol. Pharmacol.* 8:191-206.

Clevenger, M.A., D. Turnbull, H. Inoue, M. Enomoto, J.A. Allen, L.M. Henderson, and E. Jones. 1988. Toxicological evaluation of neosugar. *J. Am. Coll. Toxicol.* 7:643-662.

Rodricks, J.V. and D. Turnbull. 1987. Interspecies differences in peroxisomes and peroxisome proliferation. *Toxicol. Ind. Health* 3:197-212.

Rodricks, J.V., V.H. Frankos, D. Turnbull, and R.G. Tardiff. 1987. Risk assessment for effects other than cancer. In Felix, C.W. ed. *Food Protection Technology. Proceedings of the 1986 Conference for Food Protection.* Lewis Publishers, Inc., Chelsea, MI. pp 61-76.

Rodricks, J.V., S.L. Brown, R. Putzrath, and D. Turnbull. 1987. Use of risk information in regulation of carcinogens, in H.E. Griffin and D.V. North (eds), *Determination of No Significant Risk under Proposition 65.* California Department of Health and Welfare. pp. 18-44.

Turnbull, D. and J.V. Rodricks. 1985. Assessment of possible carcinogenic risk to humans resulting from exposure to di(2-ethylhexyl)phthalate (DEHP). *J. Am. Coll. Toxicol.* 4:111-145.

Rodricks, J.V. and D. Turnbull. 1985. Risk assessment: Biological considerations. In Milman, H.A. and Weisburger, E.K. eds. *Handbook of Carcinogen Testing.* Noyes Publications, New Jersey. pp 526-546.

Rodricks, J.V. and D. Turnbull. 1983. The use of skin penetration data in risk assessment. *CTFA Scientific Monograph Series*, No. 2 pp 71-80.

Turnbull, D., N.C. Popescu., J.A. DiPaolo, and B.C. Myhr. 1979. cis-Platinum (II) diamine dichloride causes mutation, transformation and sister chromatid exchanges in cultured mammalian cells. *Mutat. Res.* 66:267-275.

Myhr, B.C., D. Turnbull, and J.A. DiPaolo. 1979. Ultraviolet mutagenesis of normal and xeroderma pigmentosum variant human fibroblasts. *Mutat. Res.* 62:341-353.

Popescu, N.C., D. Turnbull, and J.A. DiPaolo. 1977. Sister chromatid exchange and chromosome aberration analysis using several carcinogens and non-carcinogens. *JNCI* 53:289-293.

Arlett, C.F., D. Turnbull, S.A. Harcourt, A.R. Lehmann, and C.M. Colella. 1975. A comparison of the 8-azaguanine and ouabain-resistance systems for the selection of induced mutant Chinese hamster cells. *Mutat. Res.* 33:261-278.

Turnbull, D., 1974. A comparison of the 8-azaguanine- and ouabain-resistance mutation systems with ethyl methanesulphonate and methyl methanesulphonate. *Heredity* 33:449 (Abstract).

October 15, 1997

End Submission